The role of audiovisual integration in reading acquisition: Insights from multimodal functional neuroimaging

Thesis (cumulative thesis)
Presented to the Faculty of Arts and Social Sciences
of the University of Zurich
for the degree of Doctor of Philosophy

by Iliana Irini Karipidis

Accepted in the spring term 2017
on the recommendation of the doctoral committee:

Prof. Dr. Moritz Daum (main supervisor)
and
Prof. Dr. Silvia Brem (principal scientific supervisor)

Zurich, 2018

Abstract

Learning the associations between letters and speech sounds represents a crucial step in reading acquisition, which is impaired in children with developmental dyslexia. This dissertation project examined the emergence of audiovisual integration in the brain of prereaders at risk for dyslexia and investigated whether neurobiological differences among prereaders can predict reading skills after half a year of formal reading instruction at school. A multimodal approach was implemented, including behavioural assessments, a computerized simulation of letter acquisition, and simultaneous electroencephalography–functional magnetic resonance imaging (EEG–fMRI) recordings. Following a computerized artificial-letter training, neural signatures of audiovisual integration in prereaders were significantly related not only to well-known risk factors of dyslexia but also to the rate of learning artificial letter–speech sound associations. The learning rate and brain activation involved in audiovisual integration outperformed conventional behavioural precursors of dyslexia in predicting future reading fluency. The identification of novel predictors for dyslexia not only paves the way for the development of new diagnostic assessment tools but also shows promising potential to inform the development of early intervention programs for children at risk for developmental dyslexia.

Das Erlernen der Korrespondenzen zwischen Buchstaben und Sprachlauten stellt einen zentralen Schritt im Leseerwerb dar, der bei Kindern mit einer Lese- und Rechtschreibstörung (LRS) beeinträchtigt ist. Dieses Dissertationsprojekt untersuchte die Entwicklung der Buchstaben-Sprachlaut Integration im Gehirn von Kindergartenkindern mit familiärem Risiko für eine LRS und prüfte, ob neurobiologische Unterschiede vor dem Leseerwerb die Lesefertigkeit nach einem halben Jahr schulischen Leseunterrichts vorhersagen können. Dabei wurde ein multimodaler Ansatz implementiert, der Verhaltenstests, eine computerbasierte Simulation des Buchstabenerwerbs sowie simultane Elektroenzephalographie- und funktionelle Magnetresonanztomographie-Aufnahmen beinhaltete. Die neuronale Signatur der audiovisuellen Integration nach einem Pseudobuchstaben-Training hing bei Kindergartenkindern signifikant mit bekannten Risikofaktoren der LRS zusammen sowie mit der Lernrate, mit der Assoziationen zwischen Pseudobuchstaben und Sprachlauten gelernt wurden. Die Lernrate zusammen mit einem Mass der Hirnaktivität der audiovisuellen Integration übertrafen herkömmliche Vorläuferfertigkeiten des Lesens bei der Vorhersage der zukünftigen Leseflüssigkeit. Die Identifikation neuartiger Prädiktoren für die LRS wird nicht nur die Entwicklung neuer diagnostischer Instrumente ermöglichen, sondern liefert auch Hinweise für die Entwicklung von frühen Interventionsprogrammen.

Für Brigitta,

die mir geduldig die Buchstaben beibrachte

και στον Κυριάκο,

που μας έλεγε να προσέχουμε τα κεφάλια μας

και αργότερα κατάλαβα γιατί.

Contents

Summary

Learning the associations between letters and speech sounds represents a crucial step in reading acquisition. However, children with developmental dyslexia show a severe deficit in mapping letters to their corresponding speech sounds, which can substantially hinder literacy acquisition with impairments persisting throughout adulthood. To date, the neurobiological mechanisms underlying this audiovisual integration deficit remain elusive. This dissertation project examined the initialization of audiovisual integration in the prereading brain and investigated whether neurobiological differences among prereaders can represent a proximate cause for dyslexia and thus predict future reading skills.

A sample of prereading German-speaking children at varying familial risk for developmental dyslexia was recruited and tested at the end of kindergarten (6-7 years old) and was followed up after half a year of formal reading instruction at school. A multimodal approach was implemented, including behavioural assessments, a computerized simulation of letter acquisition, and simultaneous electroencephalography–functional magnetic resonance imaging (EEG–fMRI) recordings. Functional brain responses related to audiovisual integration were measured by applying an implicit audiovisual target detection task in which trained artificial letter–speech sound correspondences were presented in either a congruent or an incongruent fashion. Based on the computerized simulation, audiovisual integration of single orthographical and phonological units was investigated, and its direct relationship to neurobiological factors, behavioural precursors, and reading outcome was assessed.

The first study of this thesis demonstrated that training correspondences of artificial letters and speech sounds initializes audiovisual integration in the prereading brain, particularly in brain regions that will later be decisively involved in reading. Brain activation was significantly related not only to familial risk for dyslexia and phonological aware-

ness skills but also to pace and performance in learning artificial letters. Based on the fMRI data, the effects of audiovisual integration were localized in temporal and parietal brain regions, mainly as increased functional responses to trained congruent associations. The EEG data, gathered in correspondence, provided new insights regarding the time course of audiovisual integration in the brain. Two event-related potentials (ERPs) showed a distinct left-lateralized posterior sensitivity for incongruently presented trained associations, one around 400 ms as pronounced posterior positivity and the second around 650 ms as reduced posterior negativity. Interestingly, the late posterior negative ERP (650 ms) was strongly related to fMRI activation in the visual cortex, corroborating the assumption of protracted visual processing in children during audiovisual integration. In short, audiovisual integration was initialized in a distributed brain network of prereading children and clearly depended on individual differences in parental risk for dyslexia, phonological skills, and the ease of learning artificial letter–speech sound correspondences.

The second study used the initialization of audiovisual integration processes in the prereading brain to identify neurobiological and behavioural factors that improve the prediction of future reading fluency. Behavioural and neural measures directly reflecting audiovisual binding of trained artificial letters and speech sounds identified future poor readers substantially more accurately than conventional assessment tools. The speed of learning artificial letters, or learning rate, proved to be the best behavioural predictor of future reading fluency skills. Prediction accuracy was increased further when the audiovisual integration in the posterior positive ERP around 400 ms and the hemodynamic responses in the left planum temporale were taken into account. Lastly, trial-wise EEG-informed fMRI analysis indicated that modulation of the superior temporal cortex by the ERP at 400 ms was significantly related to reading fluency outcome. Thus, the combined analysis of EEG and fMRI data enabled a unique coupling of neural timing and locus, reinforcing the pivotal role of the temporal cortex in audiovisual integration.

Taken together, the findings of this thesis highlight the role of audiovisual integration in reading acquisition and elucidate the emergence of the underlying mechanisms in the developing brain. Following a computerized training that simulated letter acquisition, neural initialization of audiovisual integration in prereaders was significantly related not only to well-known risk factors of dyslexia but also to the rate of learning artificial letter–speech sound associations. Importantly, the learning rate and brain activation involved in audiovisual integration outperformed conventional behavioural precursors of dyslexia in predicting future reading outcome. The identification of novel neural and behavioural predictors for dyslexia not only paves the way for the development of new diagnostic assessment tools but also shows the promising potential of innovative early and tailored intervention programs for children at risk for developmental dyslexia. In the context of educational and clinical neuroscience, directions for further studies are proposed that will be necessary to fully understand whether impaired audiovisual integration is a proximate neurobiological cause of dyslexia.

Zusammenfassung

Das Erlernen der Verbindungen zwischen Buchstaben und Sprachlauten stellt einen zentralen Schritt im Leseerwerb dar. Kinder mit einer Lese- und Rechtschreibstörung (LRS) zeigen jedoch ein schwerwiegendes Defizit bei der Zuordnung von Buchstaben zu den ihnen korrespondierenden Sprachlauten, was den Leseerwerb erheblich und mit anhaltenden Beeinträchtigungen bis ins Erwachsenenalter behindern kann. Die neurobiologischen Mechanismen, die diesem audiovisuellen Integrationsdefizit zugrunde liegen, sind bislang schwer zu erfassen. Dieses Dissertationsprojekt untersuchte die Initialisierung der audiovisuellen Integration im Gehirn von Kindergartenkindern und prüfte, ob neurobiologische Unterschiede vor dem Leseerwerb eine unmittelbare Ursache der LRS darstellen und somit die zukünftige Lesefertigkeit vorhersagen.

Eine Stichprobe von deutschsprachigen Kindern mit unterschiedlichem familiären Risiko für eine LRS wurde am Ende des zweiten Kindergartenjahres rekrutiert und getestet sowie auch nach einem halben Jahr schulischen Leseunterrichts längsschnittlich untersucht. Dabei wurde ein multimodaler Ansatz implementiert, der Verhaltenstests, eine computerbasierte Simulation des Buchstabenerwerbs und simultane Elektroenzephalographie–funktionelle Magnetresonanztomographie (EEG–fMRT)-Aufnahmen beinhaltete. Funktionelle Hirnaktivität, die mit audiovisueller Integration zusammenhängt, wurde mittels einer impliziten audiovisuellen Zielreizerkennungsaufgabe gemessen. Dabei wurden trainierte Korrespondenzen von Pseudobuchstaben und Sprachlauten entweder kongruent oder inkongruent präsentiert. Aufgrund der computerbasierten Simulation konnte die audiovisuelle Integration einzelner orthographischer und phonologischer Einheiten untersucht werden und ihr direkter Zusammenhang zu neurobiologischen Faktoren, Vorläuferfertigkeiten des Lesens und der späteren Lesefertigkeit ermittelt werden.

Die erste Studie dieser Doktorarbeit zeigte, dass das Erlernen von Assoziationen zwischen Pseudobuchstaben und Sprachlauten audiovisuelle Integration in Gehirnen von Kindergartenkindern initialisierte, insbesondere in Gehirnregionen, die später massgeblich beim Lesen beteiligt sein werden. Die Gehirnaktivität hing nicht nur mit dem familiären Risiko für eine LRS und der phonologischen Bewusstheit signifikant zusammen, sondern auch mit der Geschwindigkeit und Leistung beim Erlernen von Pseudobuchstaben. Basierend auf den fMRT Daten wurden Effekte audiovisueller Integration in temporalen und parietalen Gehirnregionen lokalisiert, hauptsächlich als erhöhte funktionelle Aktivität für trainierte kongruente Korrespondenzen. Die simultan erhobenen EEG Daten lieferten neue Einblicke in den Zeitverlauf der audiovisuellen Integration im Gehirn. Zwei ereigniskorrelierte Potentiale (EKP) zeigten eine deutliche links lateralisierte Sensitivität für inkongruent präsentierte trainierte Assoziationen: das erste etwa um 400 ms als eine ausgeprägte posteriore Positivität und das zweite etwa um 650 ms als eine verminderte posteriore Negativität. Interessanterweise hing das späte posteriore negative EKP (650 ms) stark mit der fMRT-Aktivierung im visuellen Kortex zusammen. Dieser Befund bestätigt die Annahme einer verzögerten visuellen Verarbeitung bei Kindern während audiovisueller Integration. Zusammenfassend wurde audiovisuelle Integration bei Kindergartenkindern in einem verbreiteten Hirnnetzwerk initialisiert und war deutlich abhängig von individuellen Unterschieden im elterlichen Risiko für eine LRS, in der phonologischen Bewusstheit und in der Leichtigkeit, Korrespondenzen zwischen Pseudobuchstaben und Sprachlauten zu lernen.

Die zweite Studie nutzte die Initialisierung der audiovisuellen Integrationsprozesse in den Gehirnen von Kindergartenkindern, um neurobiologische Faktoren und Verhaltensmasse zu identifizieren, die die Vorhersage zukünftiger Leseflüssigkeit verbessern. Verhaltensmasse und neuronale Masse, die direkt die audiovisuelle Integration von trainierten Pseudobuchstaben und Sprachlauten widerspiegeln, identifizierten zukünftige schwache LeserInnen wesentlich genauer als herkömmliche Einschätzungsinstrumente. Die Geschwindigkeit Pseudobuchstaben zu lernen (Lernrate) erwies sich als das beste Verhaltensmass für die Vorhersage der zukünftigen Leseflüssigkeit. Die Genauigkeit der Vorhersage wurde weiter erhöht, wenn die audiovisuelle Integration im posterioren positiven EKP um 400 ms und die hämodynamischen Reaktionen im linken Planum temporale berücksichtigt wurden. Schliesslich wies eine single-trial EEG-informierte fMRT-Analyse darauf hin, dass die Modulation des superioren Temporalkortex durch das EKP um 400 ms signifikant mit der späteren Leseflüssigkeit zusammenhing. Somit ermöglichte die kombinierte Auswertung der EEG und fMRT Daten eine einzigartige Kopplung zeitlicher und räumlicher neuronaler Informationen, welche die ausschlaggebende Rolle des Temporalkortex in der audiovisuellen Integration verstärkte.

Zusammengenommen betonen die Befunde dieser Doktorarbeit die Rolle der audiovisuellen Integration beim Leseerwerb und erläutern die Entstehung der ihr zugrunde liegenden Mechanismen im sich entwickelnden Gehirn. Nach einer Simulation des Buchstabenerwerbs in Form eines computerisierten Trainings hing die neuronale Initialisierung der audiovisuellen Integration bei Kindergartenkindern signifikant mit bekannten Risikofaktoren der LRS zusammen sowie mit der Lernrate, in der Assoziationen zwischen Pseudobuchstaben und Sprachlauten gelernt wurden. Von Bedeutung war auch, dass die Lernrate und die Hirnaktivität, die bei der audiovisuellen Integration beteiligt war, herkömmliche Vorläuferfertigkeiten des Lesens bei der Vorhersage zukünftiger Lesefertigkeit übertrafen. Die Identifikation neuartiger neuronaler und Verhaltens-Prädiktoren für die LRS wird nicht nur die Entwicklung neuer diagnostischer Instrumente ermöglichen, sondern zeigt auch ein versprechendes Potential für innovative frühe und individuell zugeschnittene Interventionsprogramme für Kinder mit einem familiären Risiko für eine LRS. Im Kontext bildungsbezogener und klinischer Neurowissenschaften werden mögliche Richtungen für zukünftige Studien vorgeschlagen, die notwendig sein werden um gänzlich zu verstehen, ob eine beeinträchtigte audiovisuelle Integration eine unmittelbare neurobiologische Ursache der LRS ist.

Acknowledgments

First of all I would like to express my gratitude to Prof. Silvia Brem for giving me the opportunity to work in the Developmental Neuroimaging group and for trusting me with this PhD project. I am especially grateful for the exemplary supervision that I received throughout my doctoral studies, the expertise she shared, and her tireless professional and personal support. Her continuous mentoring promoted my development as a researcher and her devotion to our work was a constant source of inspiration.

I am grateful to Prof. Moritz Daum who accepted to be the head of my thesis committee. I particularly appreciate his constant interest in our work that enabled the constructive exchange with his research group at the Department of Psychology.

I would like to thank Prof. Urs Maurer for his support during the past four years in Zurich and later from Hong Kong. I always enjoyed the inspiring discussions with him and his former PhD students.

I would also like to thank Prof. Daniel Brandeis who due to his immense experience and knowledge gave me exceptional advice whenever it was needed.

Moreover, it is a pleasure to thank Prof. Dr. med. Dipl.-Psych. Susanne Walitza for her tireless engagement for clinical research and her genuine interest in our project and my career. Together with all the employees of the Department of Child and Adolescent Psychiatry and Psychotherapy she provided an excellent working environment and culture.

Words are not enough to acknowledge my colleague Georgette Pleisch for the joint execution of this project, her professionalism, the guidance in EEG analysis, her knowledge on working with children, her patience, and her team-spirit. Over the past four years, we shared experiences and ideas, countless responsibilities, enthusiasm and concerns, an office and occasionally hotel rooms, long weekends at the MR-Centre, not to mention many unforgettable moments. Thank you for everything!

I am indebted to all the members of the Lexi project. In particular, I would like to thank Dr. Christoph Hofstetter, Margot Raith, and Martina Röthlisberger for their important contributions to our project. I was very lucky to have worked with several talented students and interns: Tilla Aegerter, Franziska Aepli, Lara Barblan, Anina Bauer, Christian Brauchli, Alexandra Brem, Dario Dornbierer, Nada Frei, Melanie Fuentes, Lea Götze, Charlotte Huber, Vera Keller, Fabienne Mergen-Felten, Lukas Meyer, Sonja Peteranderl, Ramona Rossi, Claudia Schneider, Simon Suter, Lia Vogel, Martina Waser, and Corinne Zurfluh. Their high commitment and pleasant company were invaluable for my PhD.

I am also grateful to Dr. Philipp Stämpfli for his essential support in the MR-Centre and to Dr. des. Stefan Sommer for his background-help during the recordings.

Further, I wish to thank Dr. med. Gregor Berger, Dr. Isabelle Häberling, Marco Hartmann, Hannah Mehringer, Yu Jin Ressel, Dr. Alexander Roth, Julia Werhahn, and David Willinger for the pleasant collaboration and the fruitful discussions over lunch and coffee breaks. I am also thankful to Etna Engeli and Franziska Minder for the regular and lively exchange.

My special thanks also go to my former colleagues Dr. Tobias Hauser for sharing his scientific knowledge and experiences, Dr. Reto Iannaccone for his tips and tricks, Dr. Jens Kronschnabel for handing over the dyslexia reigns so successfully, Anthony Schläpfer for always being so helpful, and Maya Schneebeli for her invaluable assistance to our project.

I can’t forget to mention the encouragement I received from Prof. Martha Koukkou and her family to pursue a PhD in clinical neuroscience. Thank you for the lively discussions on child development and on why doing MRI is not enough.

For being positive, and sometimes negative, role models, I am thankful to the "old Greek guard" of doctors including Agis, Akis, Anthi, Antonis and Marianna, Dimitris K., Dimitris M., Giorgos and Mirjana, Ilias, Vassilis, Viton and Stella, and particularly to Christos for his comments on my thesis. Many thanks also go to my friends Barbara, Kimon, Kriton, Nora, Orlando, Severina, and Stavroula for their loyal support in the past four years. A big thank you to Jan, Judith, Jonas, Manu, Mattis, Mazo, Mirko, Sandra, Sven, Tamara and Tobi, who helped me keep a work-life-balance. My thanks also belong to my friends from Athens and the SCS-gang for all the entertaining evenings and the regenerating trips.

My warmest thank-you belongs to my family. Above all, I would like to thank Markus for his loving support, his never-ending patience, and for simply keeping our fridge full. I am deeply grateful to Brigitta and Ursula for their continuous encouragement, and to Christina who always kept a balance between being reassuring and concerned.

This work wouldn't have been possible without the children and their families who volunteered to participate in our study. I would like to thank all the families for their high commitment to our project and all the children for their curiosity and eagerness, which made my PhD so joyful!

1 General Introduction

Our ability to read allows us to receive information and to communicate. In the digital era we live in, mobile devices enable access to written text to more people around the world than ever before (West & Chew, 2014). Nevertheless, a considerable number of people, 3-10% of the population, fail to master this essential skill despite access to schooling and literacy acquisition, and are diagnosed with developmental dyslexia (Snowling, 2013). Given that reading plays a key role in enhancing education and expanding knowledge, this presents an issue of great importance. Paulo Freire, who considered reading not only an act of knowledge but also an act of creation, described the dynamic process of reading acquisition:

> Reading the world always precedes reading the word, and reading the word implies continually reading the world. . . . In a way, however, we can go further, and say that reading the word is not preceded merely by reading the world, but by a certain form of *writing* it or *re-writing* it, that is, of transforming it by means of conscious practical work. For me, this dynamic movement is central to the literacy process. (Freire & Slover, 1983, pp. 10)

Freire's philosophical discourse demonstrates that the importance of literacy acquisition goes beyond the practical necessities of everyday life. Literacy, and thus reading, not only offers knowledge but also enables human progress through its dynamic nature and creative power. Therefore, individuals with dyslexia are deprived of the crucial opportunities that reading acquisition presents. In addition, dyslexia has severe psychosocial consequences, such as elevated motivational and emotional vulnerability in school (Poskiparta, Niemi, Lepola, Ahtola, & Laine, 2003), heightened risk for depression and anxiety disorder (Mugnaini, Lassi, La Malfa, & Albertini, 2009), and increased school drop-out and suicide rates (Daniel et al., 2006). Educational disadvantages and mental health risks emphasize the relevance of further understanding the mechanisms that cause dyslexia. Filling this research gap has highly relevant implications and could eventually improve early identification of and intervention for children with dyslexia.

1.1 Typical and atypical reading development

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013), dyslexia is a specific learning disorder with impairment of reading and/or written expression. The main symptoms are inaccurate and dysfluent reading, poor decoding skills, and spelling problems (APA, 2013). Difficulties in word reading are reported to indicate impairment in mapping letters to speech sounds (APA, 2013). These symptoms are behavioural manifestations of the developmental disorder, which has a neurobiological origin (APA, 2013). However, the neurobiological factors that impede normal reading development have yet to be clearly elucidated.

1.1.1 Neurobiological mechanisms of reading

Exploring dyslexia as a neurodevelopmental disorder begins with understanding the neurobiological mechanisms required for successful reading acquisition. From an evolutionary perspective, reading is a very recent invention, so the human brain does not possess cortical or subcortical regions specifically refined to master the challenging cognitive and perceptual demands of reading. The neural recycling hypothesis states that the human brain reuses existing neural systems for cultural inventions (Dehaene & Cohen, 2007). Hence, cultural learning relies on synaptic plasticity (Hebb, 1949) allowing cortical systems that support evolutionarily older functions to reorganize to accommodate the newly required functions (Dehaene & Cohen, 2007). Given that neural plasticity is most efficient during childhood and declines with age, it has been proposed that the cause of neurodevelopmental disorders might by an abnormal hyperplasticity in neural circuits and networks (Pascual-Leone et al., 2011).

In order to identify neurodevelopmental abnormalities leading to dyslexia, it is essential to understand the cortical reorganization processes involved in successful reading acquisition, which occur mainly in left-hemispheric brain regions (Jobard, Crivello, & Tzourio-Mazoyer, 2003). In early childhood, the dorsal temporoparietal circuit, which includes perisylvian brain regions such as the planum temporale (PT), the superior temporal gyrus (STG), and the angular gyrus, forms the basis for speech perception (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002). Within the first months of reading acquisition, neural responses in these brain regions increase during speech perception (Monzalvo & Dehaene-Lambertz, 2013), probably reflecting reading-related adaptations of linguistic structure and phonology. This temporoparietal neural circuit is retained as reading experience is gained, but its maturation continues as changes occur in the time domain of the auditory neural responses. This is reflected by neural responses that are later and more prolonged in beginning readers (200-400 ms) than in adults (100 ms; Parviainen, Helenius, Poskiparta, Niemi, & Salmelin, 2011). Therefore, despite language development being largely completed before reading acquisition, speech perception in this brain network changes with literacy, which suggests that neural reorganization related to higher phonological skills is required for reading in alphabetic languages (Jacquemot, Pallier, LeBihan, Dehaene, & Dupoux, 2003).

A proximate explanation for this reorganization of left temporoparietal brain regions is the need to facilitate the integration of letters (graphemes) and speech sounds (phonemes) for successful reading acquisition (Pugh et al., 2001). It has been proposed that audiovisual integration relies on this neural network and in particular on the superior temporal sulci (STS; Calvert, 2001). The role of the left STS as an audiovisual integration site has been confirmed in children and adults during processing of letter–speech sound associations (Blau et al., 2010; Raij, Uutela, & Hari, 2000; van Atteveldt, Formisano, Goebel, & Blomert, 2004). In line with these findings, audiovisual mismatch negativity

(MMN), an event-related potential (ERP) component around 180 ms, has been closely related to the temporoparietal brain system and the audiovisual integration of letters and speech sounds (Froyen, van Atteveldt, Bonte, & Blomert, 2008). This neural process seems to be highly fundamental and adaptive, given that readers of alphabetic languages map speech sounds to corresponding alphabetic scripts effectively, in spite of the distinct transparency and structure of different languages (van Atteveldt & Ansari, 2014). Thus, the dorsal temporoparietal circuit not only adapts to the novel phonological and linguistic demands that emerge with reading acquisition but also develops to integrate the learned associations between letters and speech sounds, which are automatized with increasing reading experience (Blomert, 2011).

Together with the dorsal temporoparietal brain system, a left lateralized posterior occipitotemporal neural circuit also undergoes pivotal reorganizational changes during reading acquisition. It includes the lateral extrastriate cortex, the fusiform gyrus (FFG), and inferior temporal regions that develop a unique visual specialization for print (Brem et al., 2010; Dehaene et al., 2010; Karin Harman James, 2010; Maurer et al., 2011). The function of this occipitotemporal brain network has been found to be strongly related to an early ERP around 170ms (N1; Rossion, Joyce, Cottrell, & Tarr, 2003), whose amplitude and latency continuously decrease into adulthood, which suggests a protracted development of visual specialization for print (Brem et al., 2006). With increasing reading experience, visual word processing in the ventral occipitotemporal (vOT) system becomes faster, enabling highly automated retrieval of the associated phonological and semantic content (Schlaggar & McCandliss, 2007).

This automatization is possibly related to a hierarchical functional reorganization within this vOT brain network, which exhibits an increasing sensitivity to print, along with higher-level processing demands, from posterior to anterior areas of this brain region (Brem et al., 2009; Thesen et al., 2012; Vinckier et al., 2007). While a more posterior site of the vOT cortex has been discussed as the letter-form area due to its selective functional response to semantic-free letter strings (Thesen et al., 2012), a more anterior occipitotemporal region has been defined as the visual word form area (VWFA) based on its word-selective function (Cohen et al., 2000; McCandliss, Cohen, & Dehaene, 2003). These spatially distinct functional patterns may arise because the anterior parts of the occipitotemporal system are not limited to mere orthographic processing but are also involved in phonological processing during reading (Zhao et al., 2016). Additionally, it has been proposed that the vOT cortex plays an important role in matching visual inputs with corresponding phonological representations, because it directly receives top-down input from higher-order phonological neural systems (Price & Devlin, 2011).

Along with the well-studied development of the dorsal temporoparietal and vOT systems, the left anterior inferofrontal region also contributes to successful reading, but its specific function remains less well understood (Ozernov-Palchik & Gaab, 2016). It has been suggested that the left inferior frontal cortex supports semantic (Carota, Kriegeskorte, Nili, & Pulvermüller, 2017; Poldrack et al., 1999) and morphosyntactic processing (Regel, Kotz, Henseler, & Friederici, 2017; Tyler et al., 2011). During reading acquisition, the inferior frontal gyrus (IFG), in concert with the left temporoparietal brain network, is thought to support the mapping of speech sounds to letters (Sandak, Mencl, Frost, & Pugh, 2004). This assumption is underpinned by the positive relationship found in readers between phonological awareness skills, requiring graphophonological decoding, and fractional anisotropy in the left arcuate fasciculus, which connects the temporoparietal system and the IFG (Vandermosten et al., 2012).

In summary, the core reason for these important neural adaptations during reading acquisition is the process of learning to map familiar phonological information to novel, arbitrary orthographic information. First, the pre-existing temporoparietal system is modified during reading acquisition to allow audiovisual integration of newly learned letter characters with speech sounds (Blomert, 2011). Second, learning letter–speech sound associations leads to a neural specialization of the left vOT system for print, which develops into the visual reading system

(Brem et al., 2010; Lochy, Van Reybroeck, & Rossion, 2016). Third, the left anterior inferofrontal system also seems to develop substantially to support cognitive demands related to reading (Sandak et al., 2004). Finally, there is anatomic evidence that these brain systems do not operate independently but work in concert (Vandermosten et al., 2012), contributing as a distributed neural network to successful reading.

1.1.2 Risk factors and predictors of developmental dyslexia

Up to now, a range of behavioural, environmental, genetic, and neurobiological risk factors have been proposed, not only in an effort to understand the etiology of dyslexia but also to identify meaningful predictors of reading impairments. Dyslexia is known to run in families, with substantial genetic hereditability (Fisher & DeFries, 2002; Paracchini, Scerri, & Monaco, 2007). In children at familial risk, the prevalence of dyslexia is 30-65% (Pennington & Lefly, 2001; Scarborough, 1990) and therefore much higher than in the general population. However, it is important to consider the interrelation of genetic and environmental risk factors. Children at familial risk for dyslexia are more likely to show additional environmental risk factors, such as poor home literacy environment (Dilnot, Hamilton, Maughan, & Snowling, 2017; Torppa et al., 2007; van Bergen, de Jong, Maassen, & van der Leij, 2014). In addition, comorbidities of dyslexia and other developmental disorders, such as preschool language impairment (Gooch, Hulme, Nash, & Snowling, 2014) and dyscalculia (Dirks, Spyer, van Lieshout, & de Sonneville, 2008), are common and present further risk factors for dyslexia (Bishop & Snowling, 2004).

A large number of studies has focused on identifying behavioural risk factors of dyslexia in prereading children. The most prominent predictors among common prereading skills are letter–speech sound knowledge, phonological awareness, and rapid automatized naming (RAN; Ozernov-Palchik & Gaab, 2016). Letter–speech sound knowledge provides a measure of the ability to associate phonology with orthography and has been repeatedly reported as one of the best predictors of reading achievement in children (Blaiklock, 2004; Elbro, Borstrøm, & Petersen, 1998; Gallagher, Frith, & Snowling, 2000;

Lyytinen et al., 2006; McBride-Chang, 1999; Wagner, Torgesen, & Rashotte, 1994). However, an impairment in letter–speech sound knowledge is only detectable shortly before the onset of reading acquisition. This is because earlier, children do not yet possess an explicit knowledge of letters, and later, all children successfully learn the letter–speech sound correspondences independent of their reading skills (Ozernov-Palchik & Gaab, 2016; Schatschneider, Fletcher, Francis, Carlson, & Foorman, 2004).

Letter–speech sound knowledge is closely related to phonological awareness, the ability to recognize and manipulate the subunits of spoken language (Ziegler & Goswami, 2005). Phonological awareness is an important predictor of reading outcome, because it comprises the phonological decoding and recoding skills needed to successfully map speech sounds to orthographic units (Elbro et al., 1998; Landerl et al., 2013; Lyytinen et al., 2006; Wagner et al., 1994). In dyslexia, phonological awareness deficits persist into adulthood (Pennington, Orden, Smith, Green, & Haith, 1990) and have been particularly reported as a predictor for word reading accuracy (Tilanus, Segers, & Verhoeven, 2013).

A further well-studied predictor of reading, RAN, measures sequential naming speed for visual stimuli, such as colors, objects, digits, or letters, across alphabetic languages (Landerl et al., 2013). It has been described as a fluency measure, and deficient RAN in children seems to be associated with a lack of graphophonological automaticity (Norton & Wolf, 2012). Specifically, impaired RAN has been found to predict dysfluent reading (Lyytinen et al., 2006), a core deficit of dyslexic readers that persists into adulthood (Norton & Wolf, 2012). Hence, while the predictive value of phonological awareness is related to reading accuracy, RAN strongly predicts reading efficiency (Tilanus et al., 2013).

In an effort to integrate the insights of the diverse behavioural precursors available, it has been proposed that the core deficit of dyslexic readers lies in the inability to audiovisually integrate letters and speech sounds (Blomert, 2011; Hahn, Foxe, & Molholm, 2014). Evidence-based intervention programs focus on this audiovisual binding deficit and by means of phonics explicitly train the associations between letters and speech sounds (Fraga González, Žarić, Tijms, Bonte, & van der Molen, 2017; Galuschka, Ise, Krick, & Schulte-Körne, 2014; Lyytinen, Ronimus, Alanko, Poikkeus, & Taanila, 2007). However, the predictive potential of this deficit has received almost no attention so far, despite its effectiveness in predicting the outcome of reading interventions (Aravena, Tijms, Snellings, & van der Molen, 2016).

In sum, the behavioural precursors discussed above have been shown to represent crucial risk factors for later reading achievement. Additionally, they have been used to successfully predict the future reading outcomes of prereading children. However, a clinical application of these precursors is not yet feasible, because the prediction models available indicate a significant lack of sensitivity, leading to an underidentification of children who will develop dyslexia (Puolakanaho et al., 2007). Accounting for the letter–speech sound binding deficit has been shown to markedly facilitate classification of children with reading impairment (Willems, Jansma, Blomert, & Vaessen, 2016). Thus, a more direct measure of the audiovisual integration deficit could offer a more reliable and useful predictor for dyslexia.

1.1.3 In search of an audiovisual neuromarker for dyslexia

A thorough understanding of the neural mechanisms enabling letter–speech sound integration is required to address the roots of the audiovisual integration deficit in dyslexia (Hahn et al., 2014). However, few neuroimaging studies have directly examined letter–speech sound binding in dyslexic and normal readers. The most frequently used paradigms in such studies experimentally manipulate the congruency of letter–speech sound pairs to operationalize audiovisual integration. The presentation of correctly paired, congruent, and incorrectly paired, incongruent, correspondences allows an (in)congruency difference to be calculated, and this provides a method of quantifying the extent of audiovisual integration (van Atteveldt et al., 2004). Additionally, and especially in ERP studies, audiovisual oddball paradigms are used to measure the electrophysiological expressions of these integration processes. In audiovisual oddball paradigms, rare speech sound stimuli, oddballs, in a sequence of frequent congruent letter–speech sound pairs, standards, evoke distinct electrophysiological responses due to automatic detection of the rare deviation. In contrast to unimodal auditory oddball paradigms, the deviation of the auditory oddball in the audiovisual variant is enhanced by its incongruency to the unchanging visual standard (Froyen et al., 2008). The application of these paradigms has enabled the comparison of audiovisual integration processes of dyslexic readers with control subjects.

A functional magnetic resonance imaging (fMRI) study comparing Dutch adult dyslexic readers with normal readers provided evidence that audiovisual integration in the superior temporal cortices is reduced in dyslexia (Blau, van Atteveldt, Ekkebus, Goebel, & Blomert, 2009). While normal readers showed significantly stronger neural responses bilaterally in the STG to congruent letter–speech sound pairs than incongruent ones, dyslexic readers did not (Blau et al., 2009). In addition, hemodynamic responses to congruent pairs were significantly reduced in the STG for dyslexic readers compared with normal readers (Blau et al., 2009). This fMRI finding highlights that a reduced engagement of the STG, taking the form of an absent congruency effect, might represent a neural manifestation of the audiovisual integration deficit in dyslexia. Interestingly, the congruency sensitivity of the superior temporal cortex to some extent depends on the transparency of the alphabetic language. Given the differing audiovisual demands of languages with higher orthographic depth, normal readers of English indicate the opposite pattern in the STG, namely an incongruency effect, which has been attributed to their reduced reliance on the transparency of single grapheme–phoneme correspondences (Holloway, van Atteveldt, Blomert, & Ansari, 2015). It remains to be investigated how the transparency of letter–speech sound pairs affects audiovisual integration processes in the superior temporal cortices of dyslexic readers.

The reduced functional involvement of the parietotemporal brain regions in dyslexia has also been demonstrated with an audiovisual lexical decision task involving congruent audiovisual presentation of German words and pseudowords (Kast, Bezzola, Jäncke, & Meyer, 2011). Dyslexic readers showed reduced neural responses in the left supramarginal gyrus and the right STS regardless of lexicality (words vs. pseudowords) and modality (auditory vs. visual vs. audiovisual; Kast et al., 2011). The absence of a modality effect in these regions complicates a clear interpretation of the findings. Nevertheless, the authors argue that the effects they report in the temporoparietal regions may be a result of deficient word decoding in dyslexics (Kast et al., 2011), which is closely related to the audiovisual integration of phonological and orthographical units.

The fMRI evidence that dyslexic adults show an audiovisual integration deficit is nicely complemented by ERP findings. In an electroencephalography (EEG) study with English-speaking adults, audiovisual integration was measured using an audiovisual oddball paradigm, including incongruent presentation of letters and letter names that were highly confusable due to either their visual similarity (e.g. p and /q/) or their phonological similarity (e.g. k and /q/; Jones, Kuipers, & Thierry, 2016). While normal readers showed stronger phonological mismatch responses (PMN: 320-380 ms) to these deviant pairs than to standards, this effect was absent in dyslexic readers. Instead, in dyslexic readers, a later lateralized readiness potential (LRP, 400-600 ms) was higher for visual deviants than for standards (Jones et al., 2016). The authors suggest a delayed processing in dyslexia, which could be caused by a lack of automatization in accessing learned representations (Jones et al., 2016).

Studies of the adult brain cannot readily disentangle the neurobiological causes and consequences that lead to an audiovisual integration deficit in dyslexia. Neuroimaging studies with children and adolescents do not fully overcome this disadvantage, but they do provide interesting findings that can be directly linked to specific developmental stages. For instance, the finding of a congruency effect in the temporal cortices of normal-reading adults but not dyslexics (Blau et al., 2009) was replicated in a group of nine-year old Dutch-speaking children (Blau et al., 2010). While normal-reading children showed an enhanced activation for congruent compared with incongruent letter–speech sound pairs in the left PT and bilaterally in the STS, this difference was absent in dyslexic children (Blau et al., 2010). Thus, this congruency effect does not seem to be the result of years-long reading experience but is already present within the first few years of reading acquisition.

Along with the temporal cortex, effects of audiovisual integration have also been reported in occipitotemporal brain regions (Kronschnabel, Brem, Maurer, & Brandeis, 2014; McNorgan, Randazzo-Wagner, & Booth, 2013). In an fMRI study, eight- to thirteen-year-old English-speaking children with and without reading difficulties solved an audiovisual rhyme judgement task (McNorgan et al., 2013). Although no significant difference was found between congruent (rhyming) and incongruent (non-rhyming) pairs, the congruency difference in the FFG and posterior STS correlated significantly with performance in an elision task (McNorgan et al., 2013), which required phoneme segmentation skills. This correlation effect was only found for normal-reading children and was driven by enhanced hemodynamic responses to incongruent pairs with increasing performance in the elision task (McNorgan et al., 2013).

Another study with 16-year old German-speaking adolescents with and without dyslexia emphasizes how divergent audiovisual integration findings are regarding the direction of the congruency sensitivity (Kronschnabel et al., 2014). During audiovisual processing of letter–speech sound associations, normal-reading adolescents showed stronger hemodynamic responses for incongruent stimuli than for congruent ones in the left inferior occipital gyrus and a marginal effect in left inferior temporal gyrus (ITG) within the occipitotemporal brain network (Kronschnabel et al., 2014). For three-letter consonant-vowel-consonant strings (CVCs), normal readers showed significant incongruency effects in the left ITG, along with the left precentral gyrus, the right postcentral gyrus, the left middle temporal gyrus (MTG), and the bilateral STG (Kronschnabel et al., 2014). This incongruency difference was also evident in the ERP data as greater negativity over temporal electrodes around 200 ms (N1) for congruent pairs than for incongruent ones (Kronschnabel et al., 2014). Dyslexic readers did not show the extensive congruency sensitivity found for normal readers. One of the few exceptions was located in the bilateral STG, in which dyslexic readers showed significantly stronger neural responses to congruent CVCs than to incongruent CVCs (Kronschnabel et al., 2014). Thus, the neural pattern found in adolescent dyslexic readers does not support the notion of a complete lack of audiovisual integration processes in the temporal cortex but points to an inverse congruency sensitivity.

Further interesting evidence on differences between normal-reading and dyslexic children in audiovisual integration comes from ERP studies. While normal-reading children have been shown to exhibit more pronounced MMN amplitudes during an audiovisual oddball task than during a unimodal auditory oddball task (Froyen, Bonte, van Atteveldt, & Blomert, 2009), dyslexic children do not show this amplitude enhancement during the concurrent presentation of the visual information (Froyen, Willems, & Blomert, 2011). This effect of reduced MMN amplitudes in Dutch dyslexic readers strongly resembled the finding in younger beginning readers (Froyen et al., 2009), indicating that dyslexic children do not develop the expected automatized integration of letters and speech sounds (Froyen et al., 2011). In addition, it has been reported that longer MMN latencies (100-250ms) in nine-year-old Dutch children correlate with higher reading fluency and accuracy (Žarić et al., 2014) and can predict reading gains after a six-month intervention focusing on letter–speech sound binding (Žarić et al., 2015). However, findings regarding MMN latencies seem to be rather inconsistent. In a study with German-speaking children of the same age, longer MMN latencies were related to impaired reading fluency and naming speed (Moll, Hasko, Groth, Bartling, & Schulte-Körne, 2016).

Similarly controversial findings have also been reported regarding a late negative ERP component (600-750ms) also known to be associated with audiovisual integration in children (Froyen et al., 2009; Froyen et al., 2011; Žarić et al., 2014). On the one hand, intensive letter–speech sound training of Dutch-speaking dyslexics resulted in reading gains and led to earlier latencies and enhanced amplitudes of the late negativity (Žarić et al., 2015). Conversely, it has been reported that German-speaking dyslexic children show significantly enhanced negative amplitudes in this late time window compared with normal readers and an atypical right lateralization, which significantly correlated with reading fluency impairment (Moll et al., 2016). These partially contradictory results highlight the need for further studies with children and disclose the importance of considering all relevant information when drawing conclusions, such as the effects of language transparency, age, and experimental paradigm.

Recently, the hypothesis of a letter–speech sound integration deficit has been challenged by an ERP study with English-reading children (Nash et al., 2017). Electrophysiological responses during audiovisual integration of letters and speech sounds in dyslexic readers were comparable with those of a younger, reading-level matched control group (Nash et al., 2017). The authors argue that the electrophysiological differences between dyslexic and normal readers found in previous studies are a result of reduced reading experience rather than evidence of a letter–speech sound integration impairment (Nash et al., 2017). When interpreting these results, the low transparency of the English language should be considered; readers of intransparent languages may rely less on audiovisual integration processes and the underlying neural processes might differ substantially (Holloway et al., 2015). Importantly, the authors of this study were unable to test their assumption directly, because they did not include a sample of reading-naïve children, which would have been needed to directly test whether the audiovisual integration deficit in dyslexia is indeed a cause of the learning disorder or merely a consequence of reduced and poor reading experience.

Taken together, there is substantial proof of an audiovisual integration deficit in the dyslexic brain from childhood through to adulthood. This deficit is reflected by either reduced engagement (Blau et al., 2010; Blau et al., 2009) or inverse congruency sensitivity in the temporoparietal reading network (Kronschnabel et al., 2014). In addition, and especially in young readers, essential congruency differences have also been reported in occipitotemporal regions, suggesting a lack of neural adaptation in the visual reading network (Kronschnabel et al., 2014; McNorgan et al., 2013). ERP findings suggest that early, automatic audiovisual integration is disrupted (Moll et al., 2016) or absent (Froyen et al., 2011) in dyslexic children, while later, explicit integration is increased (Moll et al., 2016). These findings support the critical role of temporoparietal regions in reading and corroborate the assumption of an automaticity deficit in audiovisual integration that is already present in young dyslexic readers.

1.1.4 Previous findings on neurobiological precursors of dyslexia

Studying the dyslexic brain with fMRI and EEG has revealed functional abnormalities in neural systems that undergo critical developmental changes during reading acquisition. However, studying readers makes it difficult to disentangle the neurobiological causes and consequences of dyslexia. To identify the neural markers that lead to reading impairments, it is important to study the brain before the onset of reading acquisition. A series of neuroimaging studies has attempted to determine early cortical developmental differences in prereaders with the aim of defining neurobiological precursors of dyslexia that predict later reading outcome. These studies have mainly focused on identifying neural alterations that are either directly related to well-studied behavioural predictors, such as phonological awareness (e.g. Raschle, Zuk, & Gaab, 2012), or to established deficits observed in dyslexic readers, such as visual word processing (e.g. Brem et al., 2013).

Studies of phonological processing with infants have shown that differences in auditory ERPs can significantly account for later prereading skills (Guttorm, Leppänen, Hämäläinen, Eklund, & Lyytinen, 2010) and reading outcome (Molfese, 2000). In particular, infants at risk who later developed poor reading skills showed pronounced right lateralized electrophysiological responses during speech processing, pointing to a functional deficit (van Herten et al., 2008) or developmental delay of the left-hemispheric linguistic system (Guttorm et al., 2005; Ozernov-Palchik & Gaab, 2016). In addition, longitudinal approaches have used mismatch response paradigms to identify neurophysiological predictors of dyslexia (e.g. van Zuijen et al., 2012). Reduced left lateralization of a late MMN ERP after 400 ms significantly increased prediction of word reading fluency after two, three, and five years of formal reading instruction at school (Maurer et al., 2009). Based on source estimation, the MMN was localized in the STG, suggesting a stronger engagement of the right temporoparietal system in prereaders as an electrophysiological precursor of dyslexia (Maurer et al., 2009).

In line with the ERP findings, fMRI has provided evidence that prereading children at risk for dyslexia show diminished phonological processing in the lingual gyrus and left temporoparietal brain regions (Raschle, Stering, Meissner, & Gaab, 2014; Raschle et al., 2012). These functional characteristics may be related to structural abnormalities in primary sensory cortices, because prereading children who later developed dyslexia showed reduced cortical thickness in the left Heschl's and lingual gyrus (Clark et al., 2014). A cross-sectional study provided additional evidence that structural abnormalities in temporoparietal and occipitotemporal brain regions predate dyslexia (Im, Raschle, Smith, Grant, & Gaab, 2016). Atypical sulcal patterns in these brain structures were found both in school children with dyslexia and in kindergarten children at risk for dyslexia (Im et al., 2016).

Direct evidence for the critical role of the occiptotemporal neural circuit comes from a study that investigated visual word processing longitudinally from kindergarten to second grade (Bach, Richardson, Brandeis, Martin, & Brem, 2013; Brem et al., 2013). In an implicit word processing task, future poor readers showed a stronger N1 ERP for words over the right hemisphere in kindergarten, which may reflect a developmental delay in the visual processing of print (Brem et al., 2013). In addition, functional responses during an explicit word processing task complemented these findings (Bach et al., 2013). The left-lateralized N1 print sensitivity, hemodynamic responses in the vOT cortex, and behavioural data was able to explain up to 88% of the variance in future reading skills (Bach et al., 2013). A somewhat lower but nevertheless noteworthy predictive accuracy of 80% regarding reading outcome in beginning readers was achieved based on white matter density in the left anterior arcuate fasciculus (Kraft et al., 2016).

Although studies with dyslexic adults and children have contributed to our current understanding of dyslexia as a neurodevelopmental disorder, studies with prereading children are indispensable in the search for neurobiological markers of dyslexia. EEG, fMRI, and structural MRI data have been successfully used to identify early cortical developmental differences that predict later reading success. However, longitudinal neuroimaging studies with prereaders are still rare, and several crucial neurobiological mechanisms of reading remain largely unclear. Until now, no neuroimaging study has investigated audiovisual integration of graphemes and phonemes in prereaders and evaluated the predictive value of this measure, which has shown promising results on a behavioural level.

1.2 Methods to study reading acquisition in prereaders

To date, studies with normal and impaired readers have identified candidate brain regions that have been related to the audiovisual integration deficit that characterizes dyslexia. Establishing causality between neurobiological mechanisms and observed deficits in reading requires the elimination of the confounding variable of previous reading experience. Goswami (2015) proposes a range of methods to isolate the causes of dyslexia from its consequences. Among other approaches, studies with prereaders should allow the identification of inherent impairments that lead to reading failure (Goswami, 2015). Additionally, the relevance of longitudinal study designs has been stressed, because they present the sole instrument for tracking individual learning trajectories (Goswami, 2015).

This dissertation project was embedded in a longitudinal study entitled “Neuronal markers of grapheme–phoneme training response for prediction of successful reading acquisition in children at familial risk for developmental dyslexia”. In this study, children at familial risk for developmental dyslexia were accompanied from kindergarten to second grade and were tested on a regular basis in behavioural and neuroimaging sessions. The main objectives of the longitudinal study were twofold. First, we aimed to improve prediction of reading outcome, and second, we developed and evaluated the effects of computerized phonics training, supporting struggling readers in first and second grade.

The focus of the present thesis lies on using neural markers to improve the prediction of reading success in children at familial risk for dyslexia before school enrolment. Audiovisual integration processes were examined in prereading kindergarten children, who were then followed longitudinally to determine their reading outcome. A novel approach including a simulation of letter acquisition and simultaneous EEG-fMRI recordings is proposed for studying the neurobiological mechanisms responsible for successful and failing audiovisual integration of letters and speech sounds.

1.2.1 Simulation of reading acquisition

Studying prereaders provides a research design that partly overcomes the bias of differences in reading experience (Goswami, 2015). However, prereaders already exhibit different levels of exposure to reading-related activities based on their home literacy environment (Leseman & Jong, 1998). Although kindergarten children do not yet possess explicit reading skills, they are usually familiar with some letters of the alphabet shortly before school enrolment. One way to control for these potential differences in experience and letter knowledge is to apply a simulation of reading acquisition by using an artificial script.

Short-term training of artificial scripts has been shown to successfully simulate early learning stages of reading acquisition in adults (Maurer, Blau, Yoncheva, & McCandliss, 2010; Yoncheva, Blau, Maurer, & McCandliss, 2010; Yoncheva, Wise, & McCandliss, 2015). Such training initializes neural adaptations related to reading expertise and can be used to verify in adults whether neurobiological findings in children are a result of learning processes or merely developmental effects (Maurer et al., 2010). Training-induced neural adaptations were shown to be related in particular to reading after short-term training requiring a grapheme–phoneme mapping strategy (Yoncheva et al., 2010). Therefore, directly simulating the process of learning letter–

speech sound associations provides a controlled but naturalistic setting for studying reading acquisition.

Artificial script training has also been used to identify differences in audiovisual binding between normal reading and dyslexic children (Aravena, Snellings, Tijms, & van der Molen, 2013). Although both dyslexic and normal-reading children are able to learn associations of speech sounds and artificial letters, dyslexic children make significantly more mistakes while training audiovisual matching under time pressure (Aravena et al., 2013). This finding in seven- to twelve-year old children nicely underlines the presence of an audiovisual binding deficit in dyslexia (Aravena et al., 2013). However, studying readers makes it difficult to rule out the contribution of previous reading experience to the observed deficit.

Accordingly, it is of great importance to study audiovisual integration mechanisms in prereading children without prior explicit reading experience. Using an artificial script to simulate the process of letter–speech sound correspondence learning also enables implicit reading-related experiences, such as exposure to literacy at home, to be controlled for. The artificial-letter training allows the effects of the two forms of learning to be for disentangled by focusing exclusively on explicit learning. Therefore, and based on previous findings (e.g. Maurer et al., 2010), short-term artificial-letter training seems to be an appropriate method to test for neural adaptations during early learning stages.

1.2.2 Simultaneous EEG-fMRI in pediatric neuroimaging

Advances in non-invasive neuroimaging techniques have enabled the study of brain function in pediatric samples. The well-established methods of EEG and fMRI are used to measure neural activity in normal and clinical groups of children from infancy through to adolescence. Nevertheless, each method captures different aspects of brain functioning and is associated with distinct advantages and disadvantages. Combined application compensates for several disadvantages of each method but is accompanied by additional challenges, particularly in pediatric samples.

In EEG, brain activity is measured by positioning electrodes on the scalp of a subject and the signal of each electrode is then measured against a reference electrode. One way to analyze the signal is to time-lock it to specific events (e.g. experimentally manipulated stimuli) and segment it with respect to these events to obtain ERPs. To overcome the problem of low signal-to-noise ratio in a single ERP, external stimulation is repeated several times and an average is calculated across all events (Luck, 2005). It is widely accepted that voltage differences measured on the scalp surface result mainly from postsynaptic potentials generated by pyramidal neurons (Luck, 2005). To detect such voltage changes, the simultaneous occurrence of postsynaptic potentials is needed in at least thousands of spatially aligned neurons (Luck, 2005).

ERPs provide information regarding neural processing with a very high temporal resolution, in the range of milliseconds. The time-courses of cognitive processes are usually divided into a series of ERP components (e.g. N1 or P400). Even though with high-density coverage it is possible to extract continuous signal from up to 256 electrodes, the spatial resolution of the underlying cognitive processes remains low. Source localization methods provide tools to overcome this disadvantage (Pascual-Marqui, Michel, & Lehmann, 1994). However, exact source localization is impossible, and estimations are computationally challenging, because the signal measured on the scalp can be ascribed to multiple generators in the brain. This has been described as an inverse problem with infinite solutions (Pascual-Marqui, 1999). The time-consuming preparation of the subject poses a further disadvantage of the method, although new applications have substantially reduced preparation time.

Using fMRI, neural activity can be measured by the different magnetic properties of oxygenated (diamagnetic) and deoxygenated (paramagnetic) blood. Along with changes in blood flow and volume, the processing of experimentally manipulated stimuli leads to higher demand and consumption of oxygen by specific neural populations, yielding local changes in the proportion of oxygenated and deoxygenated blood in specific brain regions (Huettel, Song, & McCarthy, 2009). In the static magnetic field (MRI scanner), these local concentration fluctuations result in a blood-oxygen-level dependent response (BOLD; Ogawa, Lee, Kay, & Tank, 1990). Intracellular recordings have provided evidence that oxygen consumption is linked to neural activity and in particular to local field potentials (postsynaptic potentials; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Thus, the fMRI signal provides an indirect measure of neural activity.

The time course of the BOLD response is described by the hemodynamic response function (HRF), which varies depending on experimental stimulation (Huettel et al., 2009). After the onset of stimulus, an initial signal dip of 1-2 s occurs due to an increase in deoxyhemoglobin. This is followed by an oxygen increase, resulting in a BOLD signal increase, which peaks after approximately 5 s. Later, neural activity and thus BOLD signal decreases, leading to a characteristic undershoot of the HRF before returning to baseline levels approximately 25 s after stimulus onset (Huettel et al., 2009). While fMRI has very high spatial resolution, in the millimeter range, it provides low temporal resolution, only in the range of several seconds. This represents a major disadvantage of the method, because it cannot capture fast dynamic processes of neural networks.

The brief description of EEG and fMRI illustrates that the two non-invasive techniques measure different aspects of brain activity. On the one hand, ERPs provide information regarding the time-course of a neural process. On the other hand, BOLD responses enable determination of which brain regions are involved in the same underlying neural process. Therefore, simultaneous EEG-fMRI recordings exploit the temporal and spatial advantages of each method. Several approaches have been proposed for merged analyses of complementary EEG and fMRI information (Huster, Debener, Eichele, & Herrmann, 2012). For instance, EEG-informed fMRI analysis is based on a trial-by-trial extraction of ERP amplitudes or latencies, which are used trial-wise to parameterize the model of the BOLD responses (Debener, Ullsperger, Siegel, & Engel, 2006; Huster et al., 2012). By entering a specific ERP feature in the fMRI analysis, it is possible to infer the source regions of this ERP (Debener et al., 2006). Thus, simultaneously combining EEG and fMRI enables the study of new aspects of cognitive processing and the underlying brain activity.

Given that both methods are highly sensitive to movement and technical artefacts, simultaneous EEG-fMRI also entails some disadvantages, such as signal losses, gradient artefacts, and cardioballistic artefacts. It is important to mention that introduction and preparation of the subjects is time-consuming, resulting in long neuroimaging sessions. Thus, challenges that have been reported for pediatric fMRI protocols, including participant cooperation and movement reduction (Bookheimer, 2000), are even more relevant when applying a simultaneous EEG-fMRI protocol in young children. Nevertheless, utilizing the simultaneous EEG-fMRI approach to study preschoolers enables unique insights to be gained into the function of the developing brain.

1.3 Aims and hypotheses

To date, the body of neuroimaging reading literature has mainly focused on examining phonological and orthographical deficits to improve characterization of dyslexia as a neurodevelopmental disorder. However, the attempt to investigate neural processes related to the audiovisual integration deficit in dyslexia has received growing attention in recent years. This increasing research interest stems from the accumulating behavioural evidence pointing towards a specific letter–speech sound deficit in prereading children at risk for dyslexia (Blomert & Willems, 2010). However, it is still unclear whether the neural deficits observed in dyslexic readers are the underlying cause of the reading disorder or a developmental consequence of poor and reduced reading practice. The current thesis attempts to investigate whether reading-related audiovisual integration processes are already evident in the prereading brain and whether children with poor reading outcomes show specific deviations in these neural processes before reading acquisition.

The first study aimed to investigate audiovisual integration processes in the brain of prereading children at risk for dyslexia. We hypothesized that a short artificial-letter training session is sufficient to initialize neural adaptations that enable audiovisual integration of single graphemes and phonemes. A central objective in studying a high-risk sample, a proportion of whom would eventually develop reading problems, was to reveal whether neurobiological mechanisms responsible for audiovisual integration are directly linked to behavioural and familial risk factors as well as to training-related measures. Thus, it was expected that the artificial-letter training would not only be able to simulate the first step of reading acquisition but would also provide early behavioural and neural indications regarding potential deficits in sufficiently mapping the trained correspondences.

The second study exploited the advantages of the longitudinal experimental design. It was hypothesized that if an audiovisual integration deficit is a proximal cause of dyslexia and can be quantified by artificial-letter training, it should be capable of predicting the reading outcome of prereaders. Based on the assumption that dyslexia is a neurodevelopmental disorder, we expected that not only training-related measures but also functional neuroimaging data of audiovisual integration would provide better prediction than common behavioural precursors. In addition, we anticipated that merging the simultaneous EEG-fMRI data would yield novel insights into the functional differences that lead to reading impairments in beginning readers.

2 Study A: Neural initialization of audiovisual integration in prereaders at varying risk for developmental dyslexia

Iliana I. Karipidis[1,2], Georgette Pleisch[1,2], Martina Röthlisberger[1], Christoph Hofstetter[1], Dario Dornbierer[1], Philipp Stämpfli[3], and Silvia Brem[1,2]

[1]Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zurich, Switzerland

[2]University of Zurich and ETH Zurich, Neuroscience Center Zurich, Switzerland

[3]MR-Center of the University Hospital for Psychiatry, University of Zurich, Switzerland

A similar version of this manuscript has been published by *Human Brain Mapping*.

First published online on 14 October 2016

Printed in February 2017 (Volume 38, Issue 2, Pages 1038-1055)

Karipidis, I. I., Pleisch, G., Röthlisberger, M., Hofstetter, C., Dornbierer, D., Stämpfli, P., & Brem, S. (2017). Neural initialization of audiovisual integration in prereaders at varying risk for developmental dyslexia. *Human Brain Mapping*, *38*(2), 1038-1055.

3 Study B: Early prediction of reading fluency: A training and multimodal neuroimaging approach

Iliana I. Karipidis[1,2], Georgette Pleisch[1,2], Daniel Brandeis[1,2,3,4], Alexander Roth[1], Martina Röthlisberger[1], Maya Schneebeli[1], Susanne Walitza[1,2,4], Silvia Brem[1,2]

[1]Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zurich, Switzerland.

[2]University of Zurich and ETH Zurich, Neuroscience Center Zurich, Switzerland.

[3]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany.

[4]Center for Integrative Human Physiology Zurich, University of Zurich, Switzerland.

A similar version of this manuscript has been published by *Scientific Reports*.

Published on 8 May 2018 (Scientific Reports 8, Article number:7121)

Karipidis, I. I., Pleisch, G., Brandeis, D., Roth, A., Röthlisberger, M., Schneebeli, M., . . . Brem, S. (2018). Simulating reading acquisition: The link between reading outcome and multimodal brain signatures of letter–speech sound learning in prereaders. *Scientific Reports*, *8*(1), 7121. doi:10.1038/s41598-018-24909-8

4 General Discussion

In this thesis, brain activity during audiovisual integration of trained graphemes and phonemes was investigated in prereading children at risk for dyslexia. An emerging adaptation of neural mechanisms for audiovisual integration was identified in prereaders and was significantly related to reading precursors (Study A). In a longitudinal analysis, the extent of this neural specialization in combination with the learning rate significantly improved prediction of reading outcome compared with conventional precursors (Study B). These results advance the current state of dyslexia research considerably, despite some limitations and the persistent need for further studies to achieve even better understanding of reading-related audiovisual integration processes. Subsequently, the findings of this thesis are discussed in a broader neuroeducational context and directions for future studies are proposed, which will be vital for addressing myriads of still outstanding research questions.

4.1 Artificial-letter training: A novel path to study reading

The studies presented above demonstrate that letter–speech sound correspondence learning can be simulated in reading-naïve kindergarten children by means of artificial-letter training. Providing a controlled experimental setting, the training allowed investigation into the neural basis of audiovisual integration at the first step of reading acquisition. Individual learning rates and functional brain activity pinpointed behavioural and neural differences respectively, the combination of which provided a reliable prediction of future reading fluency. Thus, short-term training of artificial letter–speech sound correspondences evoked plastic changes in neural circuits of interest and revealed neural and behavioural deviations in children with future reading impairment.

4.1.1 Audiovisual integration in prereaders at risk for dyslexia

In Study A, prereaders performed an implicit audiovisual integration task with the aim of inferring emerging audiovisual integration processes, following a short artificial-letter training session. Similar to previous studies, audiovisual integration was measured by presenting congruent and incongruent trained grapheme–phoneme correspondences, which allowed direct comparison between the two conditions (Blau et al., 2010; Blau et al., 2009; Holloway et al., 2015; Kronschnabel et al., 2014; van Atteveldt et al., 2004). Interestingly, parallel analyses of ERP and fMRI data revealed inverse congruency sensitivity in the two modalities. While electrophysiological responses were stronger towards incongruent stimuli, hemodynamic responses were dominated by a congruency effect with increasing learning rate and phonological awareness skills, highlighting the complementary nature of the two methods.

In the fMRI data, the congruency effect was stronger at higher learning rates in the left FFG and right STG. Hence, enhanced activation in the temporoparietal and occipitotemporal neural circuits does not appear to be a long-term consequence of reading experience but reflects the ease of learning grapheme–phoneme correspondences. This result strongly suggests a coherent link between reduced engagement of the neural reading network and difficulties in efficiently mapping graphemes and phonemes, in line with the assumption of a letter–speech sound binding deficit as a principal cause of dyslexia (Blomert, 2011),.

In addition, two ERP components were found to be significantly related to audiovisual integration of single grapheme–phoneme correspondences. Posterior left-lateralized electrophysiological responses were more positive around 400 ms and less negative around 650 ms for trained incongruent pairs. The incongruency effect of the late negative posterior ERP, whose topography closely resembled the visual N1 component, was shown to be related to brain activity in lower-level visual brain areas. This protracted visual response occurred shortly before the offset of the presented stimuli, and the sensitivity observed for trained incongruent pairs was interpreted as a delayed visual mismatch between the incorrectly presented grapheme and the correctly stored one. While this late-occurring negativity did not correlate with any behavioural measure or risk factor, the earlier positivity was significantly related to individual learning achievement and familial risk. These findings particularly highlight individual differences in automatic processing stages in the time course of audiovisual integration that could be crucial for future reading acquisition.

Importantly, the task design included a control condition of untrained grapheme–phoneme correspondences. To control for effects of visual familiarity, participants were passively exposed to the untrained graphemes. Thus, these results cannot be explained by mere perceptual differences in the primary visual and auditory cortices within the at-risk group but are clearly a result of learning processes that occurred during the artificial-letter training. In line with the hypothesis, Study A demonstrated that audiovisual integration of graphemes and phonemes can be triggered with a short artificial-letter training session, which was sufficient to evoke plastic changes in neural reading circuits as a function of training measures, familial risk factors, and behavioural precursors.

4.1.2 Predicting reading outcome based on audiovisual integration

Study B used a simulation of letter acquisition for the first time to investigate whether audiovisual integration in the prereading brain can improve prediction of future reading fluency. To complement previous studies that used early cortical developmental differences in prereaders to predict later reading success (Brem et al., 2013; Guttorm et al., 2005; Saygin et al., 2016), Study B focused on identifying neuromarkers of the audiovisual binding deficit. ERP and fMRI data indicated that subjects' later reading outcome depended significantly on their audiovisual integration as prereaders. The most pronounced differences between future normal and poor readers were found in the ERP around 400 ms and in the right MFG, the left PT, and the left vOT.

The two behavioural measures that were shown to significantly predict reading outcome were RAN and the learning rate during the artificial-letter training. Notably, reading outcome was measured with a 1-minute word and pseudoword reading fluency test, accounting for reading accuracy under time pressure. Given that both RAN and the learning rate are speed measures, their direct relationship to reading fluency is not surprising. It has been reported that various reading precursors exhibit differential effects on reading fluency and accuracy (Moll et al., 2014). Therefore, other behavioural precursors, such as phonological awareness, may be expected to provide a better prediction of reading outcome if a measure of reading accuracy is applied that does not involve time pressure. Nevertheless, Study B focused on reading fluency, because in German readers it is considered one of main and most persistent symptoms of dyslexia throughout development (Wimmer, 2006).

The higher predictive accuracy of reading fluency from the learning rate (67.9%) than from RAN (60.7%) was further increased when including either ERP or fMRI data. Specifically, audiovisual integration of the posterior left-lateralized ERP around 400 ms together with the learning rate increased prediction accuracy to 78.6%, while audiovisual integration in the left PT in combination with the learning rate reached an accuracy of 82.1%. Interestingly, two children who had a specific impairment either only in word or pseudoword reading fluency were wrongly classified as normal readers by both the ERP and fMRI prediction models. Thus, although the two modalities capture distinct aspects of audiovisual integration on a temporal and spatial domain, the individual classification by the two prediction models was similar, emphasizing that the two modalities measure common underlying neural processes.

In order to adequately merge the evidence of both modalities, an EEG-informed fMRI analysis was performed. Single-trial amplitudes of the left lateralized incongruency effect around 400 ms were significantly related to hemodynamic responses in the right STG. This allowed the source of the ERP to be pinpointed, signalling initial audiovisual integration, in the STG, a brain region that has been repeatedly mentioned to play a critical role in audiovisual integration of letters and speech sounds (Blau et al., 2010; Blau et al., 2009; Hashimoto & Sakai, 2004;

van Atteveldt et al., 2004). In essence, the application of artificial-letter training revealed emerging audiovisual integration processes in prereaders, which on a behavioural and neurobiological levels provided, as hypothesized, better predictors of reading fluency outcome than conventional reading precursors.

4.1.3 Benefits of multimodal functional neuroimaging in developmental research

This thesis was embedded in the first research project to apply simultaneous high-density EEG and fMRI in a sample of prereaders. So far, the effort to identify functional neurobiological precursors of dyslexia has focused on either EEG or fMRI recordings and has lacked crucial information regarding either the location or time-course of brain activation. The simultaneous EEG-fMRI approach presented here overcomes this problem by offering high temporal and spatial resolutions that have clearly advanced our current understanding of linguistic audiovisual integration processes in prereaders.

Given that this exact experimental setting had never been used before in children and that simultaneous EEG-fMRI represents a relatively recent methodology, no common standards yet exist for combined analyses. Here, a single-trial EEG-informed fMRI analysis was performed to infer the neural source of the ERP component around 400 ms that reflected audiovisual integration. The data analysis pipeline was specifically adapted to the needs and aims of the current project. Amplitude values derived from the ERP time window were extracted trial-wise, averaged, and standardized, before being used to model hemodynamic responses measured with fMRI. The unique combination of simultaneous high-density EEG and fMRI represents a striking novelty in the field of pediatric neuroimaging and the results evidently highlight the benefits of the multimodal functional neuroimaging approach in developmental research.

4.1.4 Limitations and outlook

Although the two studies presented in this thesis shed light on previously unknown aspects of neural adaptations related to audiovisual integration of grapheme–phoneme correspondences, some limitations need to be considered. The following section discusses the most important limitations of the studies and their possible impact on the results reported. Additionally, future studies are needed to address a range of still-unanswered research questions. The relevance of the limitations goes beyond the present thesis, and possible directions are proposed for future neuroimaging studies on reading acquisition.

The objective of this thesis was to investigate audiovisual integration processes in prereading children at varying familial risk for dyslexia. Parental reading history was assessed, and the highest risk factor among parents was used to quantify the familial risk status of each participant. Given that maternal, rather than paternal, risk has been shown to significantly influence the neuroanatomical development of reading-related brain areas (Black et al., 2012), investigating the separate contributions of maternal and paternal risk for dyslexia may provide additional insights into functional neurobiological differences and reading outcome. Future analyses attempting to uncover differences between the effects of maternal and paternal risk factors should take into account critical environmental parameters, such as family status, childcare arrangements, and regular parent-child activities.

A central limitation of the studies is that no children without familial risk for dyslexia were recruited and assessed. A future evaluation of the results presented here should include a control group with age-matched children without familial risk for dyslexia. This will clarify whether the differences between at-risk children with impaired and normal reading outcome are purely a result of an inherent audiovisual deficit in the former or also a consequence of efficient compensatory mechanisms in the latter. Data on the presence or absence of differences between children with and without familial risk who will eventually develop normal reading skills will make it possible to infer whether children at risk generally carry a neuromarker for dyslexia or not.

The relatively small sample sizes present a further main limitation and hinder a generalization of the reported findings. Sensitive and special populations, such as children at risk for a specific learning disorder, are difficult to recruit. In particular, participation in a longitudinal research study is very time-consuming for the families involved, and parents are often reluctant to consent to the application of neuroimaging techniques to their children. Additionally, studying pediatric samples is associated with limitations in recording time, leading to restrictions in data quantity. Child-friendly task designs that are specifically developed to be as simple and short as possible affect the explanatory power of pediatric neuroimaging studies. However, it is noteworthy that relatively low statistical power and thereto related reduced reliability also pose an important problem in contemporary neuroimaging studies with healthy adults (Button et al., 2013; Eklund, Nichols, & Knutsson, 2016). Thus, the need to increase effect sizes and the reproducibility of findings presents a general challenge in the field of neuroimaging. This underlines the pressing need for large-scale studies to increase statistical power and therefore external validity of reported neuroimaging findings.

Next to restrictions in data quantity, pediatric neuroimaging studies are also associated with compromises on data quality. In young children especially, interindividual differences in motivation and alertness strongly influence movement artefacts and task performance (Raschle et al., 2009). In spite of addressing these challenges in the pediatric sample used in these studies and of applying additional movement corrections, up to 33% of the neuroimaging data sets did not meet our stringent quality criteria and had to be excluded from analyses. Even though the exclusion of several data sets further reduced the size of the analyzed samples, the use of stricter exclusion criteria than in similar pediatric studies (e.g. McNorgan, Awati, Desroches, & Booth, 2014) ensured that only high-quality data sets were included in the performed analyses. In simultaneous EEG-fMRI recordings, the elimination of confounds, such as movement artefacts, is particularly relevant for an informative combined analysis of the data that can be derived from each modality.

Furthermore, sample sizes also play a crucial role in developing prediction models, because the optimism bias of a model increases with declining number of subjects and rising number of predictor variables (Whelan & Garavan, 2014). In this thesis, the number of model parameters was restricted, and leave-one-out cross-validation was performed to minimize the optimism bias and to avoid overfitting when defining prediction models. However, an exhaustive predictive model identification should also include further validation by testing the model on an independent sample (Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015). A larger sample size is required to enable the prediction model to be built on one subsample and an evaluation to be performed on another independent subsample. Future studies developing prediction models that can be generalized to independent samples will further facilitate the identification of valid neuromarkers and therefore the translation of neuroimaging findings to standard educational and clinical practice (Gabrieli et al., 2015).

Together with increased statistical power and external validity, larger sample sizes will allow adequate inference of the effects of heterogeneities expected within samples at risk for dyslexia. Dyslexia risk profiles are known to vary in regard to their associated deficits, for instance by showing a single deficit either in phonological awareness or RAN, or by exhibiting a double deficit in both precursors (Ozernov-Palchik et al., 2016). Here, small sample sizes did not permit group comparisons of children with different risk profiles nor with different outcomes, regarding word reading, pseudoword reading, and spelling deficiencies. Instead, the role of the various risk factors was tested using regression approaches. Nevertheless, a more detailed comparison of symptom-based subgroups characterized by heterogeneous learning disorder profiles seems highly relevant. Future studies with larger samples may provide a better understanding of the neurobiological deviations leading to various subtypes within the disorder, which could have important implications for the early diagnosis and treatment of dyslexia.

Given that the analyses presented here regarding audiovisual integration were embedded in a larger longitudinal study, it will be important to also incorporate findings of further stimulus types such as single letters, letter strings, and digits and unimodal visual and auditory processing in the interpretations outlined here. In addition, further longitudinal analyses should clarify the subsequent development of audiovisual integration by including neuroimaging data from multiple time points. This will be particularly important in testing the long-term effects of schooling on reading skills and neural specialization of brain circuits involved in audiovisual integration. Additional investigations on the role of audiovisual integration in associative learning should also clarify whether dyslexic children show a deficit in other domains too, such as numbers, or whether the disorder is limited to linguistic, grapheme–phoneme associations (Mourgues et al., 2016).

In sum, the methodological issues discussed here limit the interpretation of the studies' findings. Several of the limitations are directly related to the relatively small sample sizes, which present a crucial constraint in neuroimaging studies generally (Button et al., 2013). In particular, studying young pediatric populations is associated with serious limitations, which are, notwithstanding, outweighed by many advantages. Studying prereaders enables the neurobiological mechanisms of audiovisual integration to be disentangled from previous explicit reading experience. Additionally, their longitudinal follow-up allows crucial developmental stages to be examined shortly before and after the onset of formal reading acquisition (Goswami, 2015). Thus, despite the limitations, this thesis proposes a methodological framework for studying developmental disorders that provides an appropriate groundwork for future studies.

4.2 Challenges and future directions in tracking the origin of dyslexia

As outlined above, the current thesis and several previous studies have focused on understanding the neurobiological mechanisms underlying dyslexia. However, the need to identify reliable neurobiological precursors of reading outcome remains urgent. This section discusses possible directions of future studies and elaborates on the utmost importance of translating basic research findings into applications for clinical practice.

4.2.1 Extending the multimodal approach: The role of brain structure

Applying a multimodal approach is associated with the benefit of exploiting the advantages of several neuroimaging techniques. In this thesis, the combined use of EEG and fMRI certainly provided an expedient method by which to simultaneously study temporal and spatial aspects of reading-related brain activation. However, this approach does not enable conclusions to be drawn about how the functional reorganization processes are related to anatomical brain development. Neuroanatomical adaptations during reading acquisition can be measured through changes not only in grey matter and white matter volume but also in structural connectivity (Eckert, 2004). Interestingly, deviations found in the brain function of dyslexic readers seem to partly overlap with structural abnormalities (Eckert, 2004).

The interrelation of functional and structural brain measures in dyslexia is highly relevant to understanding the interplay between regions of the neural reading network. In children with varying reading abilities, functional responses in the posterior STS during an audiovisual rhyming task have been shown to be related to higher fractional anisotropy values in the arcuate fasciculus, connecting temporoparietal brain regions with the inferior frontal gyrus (Gullick & Booth, 2014). Higher white matter density in the arcuate fasciculus has also been found to correlate with enhanced right prefrontal activation during a phonological task and to significantly predict future reading gains in children with dyslexia (Hoeft et al., 2011). Thus, the interrelation of functional and structural brain properties could be highly relevant to studying prereaders and to providing a more comprehensive understanding of the neural basis of dyslexia.

Recently, it has been shown that structural connectivity of the VWFA to higher-order language areas in prereaders predicts its functional specialization (Saygin et al., 2016). It is widely accepted that the functional specialization of the VWFA emerges with reading acquisition (Brem et al., 2010; Dehaene et al., 2010). The finding that structural connectivity of the VWFA to higher-order language areas is already evident in prereaders and predicts its functional specialization decisively extends current accounts of neurobiological adaptations occurring during reading acquisition (Saygin et al., 2016). This new insight allows a further interpretation of this thesis's result regarding the emergence of the vOT specialization for audiovisual integration. It can be assumed that the functional response of this region in prereaders, which was triggered by the short grapheme–phoneme training, was based on existing structural connections of the VWFA to temporoparietal and frontal regions.

Hence, providing an account of the neuroanatomical characteristics of typical and atypical reading development appears to be highly relevant. Accordingly, adding structural brain measures to the multimodal functional neuroimaging approach would augment the vast potential of combined analysis techniques. Future studies aiming to uncover the causes and consequences of dyslexia should consider a wider use of a variety of structural and functional brain methods to account for the interdependency of brain function and structure during literacy acquisition.

4.2.2 Studying developmental trajectories with longitudinal neuroimaging approaches

Studies with children and adolescents are essential to investigate the neurodevelopmental processes occurring during reading acquisition. Studying the developing brain provides notable insights into the underlying neurobiological mechanisms. At the same time, neuroimaging studies with children pose considerable challenges. Frequently, such studies include participants of a wide age range without specifically accounting for age differences (e.g. McNorgan et al., 2013). While cross-sectional studies explicitly address age-related differences, they are limited to providing a snapshot of the individual developmental trajectories. Thus, only longitudinal studies repeatedly measuring the same subjects can provide a complete view of the progressive and dynamic nature of the human brain.

If we assume that learning and its related developmental processes are dynamic, then multiple data points are needed to establish a complete model of reading acquisition. For instance, it has been proposed that the vOT region receives top-down inputs from higher-order phonological and semantic brain regions during visual processing of print (Price & Devlin, 2011). These top-down inputs differ depending on reading expertise, resulting in lower or higher prediction errors that are linked to lower or higher neural activation respectively (Price & Devlin, 2011). Before the onset of learning and after attaining a high level of reading expertise, prediction errors are expected to be absent or very low, because in the first case, no higher-level associations have been formed, and in the latter case, the associations are almost perfectly automatized (Price & Devlin, 2011). In early learning stages, however, predictions are expected to be highly erroneous due to a lack of automatization, resulting in enhanced top-down feedback and therefore in increased neural responses (Price & Devlin, 2011). The proposed inverted U-shaped development of the visual system emphasizes the complexity of learning-related changes in neural circuits, which can only be captured with repeated measurements of intraindividual learning curves.

Therefore, when investigating the etiology of dyslexia with neuroimaging methods, developmental effects need to be tracked longitudinally from early childhood through to adulthood. Longitudinal study designs can allow neural risk markers to be distinguished from actual neurobiological predictors of dyslexia. For instance, neurobiological deviations during non-speech auditory processing have been found to be characteristic for children at risk for dyslexia but not predictive of later reading outcome (Plakas, van Zuijen, van Leeuwen, Thomson, & van der Leij, 2013). Accordingly, studies examining the anatomical basis of dyslexia have tracked developmental changes by repeatedly examining the same subjects. For example, while reduced grey matter volume in the left STG at the beginning of reading acquisition was found to be associated with reduced reading gains after one year of reading instruction in school, reading-dependent structural differences in parietal regions were a consequence of reduced reading experience (Linkersdörfer et al., 2014). Increases in white matter volume in the left temporoparietal system from kindergarten to third grade has also been related to reading proficiency (Myers et al., 2014). The predictive accuracy of this developmental effect was rather moderate (59%), but it captured the developmental changes occurring in brain networks crucial for reading.

Thus, studying the developmental trajectories of neural mechanisms is indispensable in the search for valid neuromarkers of dyslexia (Xia, Hancock, & Hoeft, 2017). Future longitudinal studies will advance our knowledge of the etiology of dyslexia and will be equally relevant to understanding normal development and to tracking neural mechanisms that lead to developmental disorders arising during childhood. Finally, studying the human brain during early childhood and following its developmental trajectories will further unravel the important role of human brain development in educational and clinical contexts.

4.2.3 Implications of artificial-letter training: Clinical and educational translation

The ultimate goal of neuroimaging studies seeking to identify reliable predictors for dyslexia is the clinical translation of their findings (Buchweitz, 2016). In spite of recent methodological and computational advances that have enabled the accumulation of considerable evidence from different populations and neuroimaging techniques, a direct translation of this evidence to improve diagnosis and treatment of dyslexia is not yet feasible. Nevertheless, insights into neurobiological processes can corroborate the understanding of behavioural manifestations related to dyslexia. Hence, developing behavioural assessment instruments that directly reflect certain neural mechanisms may have important clinical implications.

In this thesis, the learning rate in the artificial-letter training was significantly related to audiovisual integration processes in the brain, reflecting the extent of automatic integration of single graphemes and phonemes. An evaluated and refined version of the artificial-letter training could provide a useful tool for early identification of children with an audiovisual integration deficit. This would allow targeted support with intervention programs focusing on reinforcing grapheme–phoneme associations. In addition, assessments with artificial-letter training have been shown to predict responsiveness to intervention programs (Aravena et al., 2016) and could thus pave the way towards personalized treatment.

The relationship of reading skills to performance in learning associations between phonemes and arbitrary symbols was further highlighted by a recent study comparing two types of paired associate learning tasks (Mourgues et al., 2016). An adaptive paired associate learning task directly mimicking the acquisition of letter–speech sound correspondences by using characters of the Braille alphabet predicted the word and pseudoword reading skills of school children better than common behavioural measures (Mourgues et al., 2016). Interestingly, a paired association task including pictures of objects and words of a foreign language did not show the same predictive value; it only increased model fit regarding word reading outcome in combination with phonological awareness skills (Mourgues et al., 2016). These findings underline that reading skills are not generally related to learning audiovisual associations but specifically associated with mapping single orthographical and phonological units. Therefore, simulations of letter acquisition could have a great potential in practice as dynamic assessment tools.

Along with the assessment tools presented by Aravena et al. (2013; 2016) and Mourgues et al. (2016), the artificial-letter training used in this thesis is one of the first attempts to use the predictive value of grapheme–phoneme mapping for reading skills. Additionally, it was demonstrated that the artificial-letter training provides a unique tool with which to study training-induced audiovisual integration processes in the brain. Future studies should aim to further develop dynamic assessment tools and to evaluate their application in clinical and educational settings. Finally, empirical and neurobiological evidence on such dynamic assessment tools could enable tailored interventions for children with dyslexia.

4.3 Dyslexia in a cross-linguistic context and the case of German-speaking Switzerland

Although grapheme–phoneme mapping is considered crucial during reading acquisition in all alphabetic languages, differences in orthographic transparency critically influence the predictive value of behavioural reading precursors across languages (Landerl et al., 2013; Ziegler et al., 2010). Studies across alphabetic languages have led to the conclusion that readers of different languages might engage different neural circuits when processing linguistic information (Holloway et al., 2015). This relates to language-specific neural deviations in dyslexic readers (Martin, Kronbichler, & Richlan, 2016). Therefore, accounting for language-specific transparency of letter–speech sound associations seems highly relevant when investigating the neural mechanisms of audiovisual integration.

In particular, dyslexic readers of rather transparent and semitransparent orthographies, including German, have been shown to exhibit decreased brain activity in the left FFG, the left temporoparietal cortex, the left IFG (pars orbitalis), and the left frontal operculum, along with inordinately pronounced activity in the left precentral gyrus (Martin et al., 2016). For intransparent orthographies such as English on the other hand, reduced functional responses have been found in the left IFG (pars triangularis), the left precuneus, and the right STG, together with enhanced activation in the left anterior insula. These findings underline the importance of taking differences in linguistic structure across languages into consideration (Martin et al., 2016). Nevertheless, diminished activations in the left occipitotemporal cortex, including parts of the FFG, have been consistently reported across transparent and intransparent orthographies (Martin et al., 2016), indicating a universal neurobiological basis of dyslexia.

The sample examined in this thesis included German-speaking children growing up in Switzerland. The predominant use of local dialects in the German-speaking part of Switzerland results in noteworthy differences between the spoken language variety and the written language taught during reading acquisition at school. Although the use of dialect variations might influence the reading outcome of beginning readers (Terry, Connor, Thomas-Tate, & Love, 2010), little is known about the impact of local dialects on audiovisual integration processes. A recent ERP study reported that prereading children speaking the Swiss German dialect exhibit distinct mismatch effects when audiovisually processing words in Standard German that differ from the dialect-specific vocabulary (Bühler, Waßmann, Buser, Zumberi, & Maurer, 2017). Nevertheless, dialect-specific effects on grapheme–phoneme mapping and hence normal and abnormal reading acquisition remain to be further investigated.

Although the findings presented here may be restricted by the effects of language transparency and regional dialects, they might also be very useful for local policy makers. The presence of a letter–speech sound binding deficit in a considerable percentage of beginning readers in Switzerland could be relevant to assessing the suitability of teaching materials used in schools. It should be assessed which textbooks and teaching methods are particularly supportive of or impeding for children with such a specific learning disorder. For instance, the effectiveness of teaching letter–speech sound knowledge by means of pictures, illustrating facial expressions that pronounce speech sounds, should be empirically tested in respect to audiovisual integration processes. Such methods with higher audiovisual integration demands, which seem to be beneficial for normally developing children, might represent an additional obstacle for children struggling with reading acquisition.

4.4 Conclusions

The two studies presented in this thesis investigated the role of audiovisual integration in reading acquisition. Firstly, audiovisual integration of artificial letters and speech sounds was successfully initialized in prereading children and led to the emergence of reading-related neural adaptations. Secondly, neural specialization enabling audiovisual integration in prereaders increased prediction of reading fluency after half a year of formal reading instruction. These results clearly demonstrate that behavioural and neural differences in mapping letters and speech sounds predate reading acquisition and offer a better prediction of reading outcome than conventional screening instruments. Applying an innovative simulation of letter–speech sound acquisition and a state-of-the-art simultaneous EEG-fMRI protocol allowed information derived from different modalities to be combined, providing a novel framework for studying neurodevelopmental learning disorders. Future longitudinal studies should further investigate how functional and anatomical neurobiological factors during early childhood contribute to predicting later reading success across languages. A comprehensive understanding of the underlying neurobiological mechanisms could ameliorate the severe consequences of dyslexia by facilitating early identification as well as tailored support during reading acquisition.

Abbreviations

ANOVA	analysis of variance
ARHQ	adult reading history questionnaire
BOLD	blood-oxygen-level dependent
CVC	consonant-vowel-consonant
EEG	electroencephalography
ERP	event-related potential
FFG	fusiform gyrus
fMRI	functional magnetic resonance imaging
FT	frontotemporal
FWE-corr	family-wise error corrected
FWHM	full width at half maximum
GFP	global field power
GLM	generalized linear model
HRF	hemodynamic response function
ICA	independent component analysis
IFG	inferior frontal gyrus
IQ	intelligence quotient
ITG	inferior temporal gyrus
LFT	left frontotemporal
LMM	linear mixed model
LPOT	left parietooccipitotemporal
LRP	lateralized readiness potential
MFG	middle frontal gyrus
MMN	mismatch negativity
MNI	Montreal Neurological Institute

MRI	magnetic resonance imaging
MTG	middle temporal gyrus
PMN	phonological mismatch negativity
POT	parietooccipitotemporal
PT	planum temporale
RAN	rapid automatized naming
RFT	right frontotemporal
ROI	region of interest
RPOT	right parietooccipitotemporal
SE	standard error
STG	superior temporal gyrus
STS	superior temporal sulcus
TANOVA	topographic analysis of variance
Tcong	trained congruent
Tinco	trained incongruent
TR	repetition time
Ucong	untrained congruent
Uinco	untrained incongruent
vOT	ventral occipitotemporal
VWFA	visual word form area

References

Allen, P. J., Josephs, O., & Turner, R. (2000). A method for removing imaging artifact from continuous EEG recorded during functional MRI. *Neuroimage, 12*(2), 230-239.

APA. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, DC: American Psychiatric Association.

Aravena, S., Snellings, P., Tijms, J., & van der Molen, M. W. (2013). A lab-controlled simulation of a letter–speech sound binding deficit in dyslexia. *Journal of experimental child psychology, 115*(4), 691-707.

Aravena, S., Tijms, J., Snellings, P., & van der Molen, M. W. (2016). Predicting responsiveness to intervention in dyslexia using dynamic assessment. *Learning and Individual Differences, 49*, 209-215.

Bach, S., Richardson, U., Brandeis, D., Martin, E., & Brem, S. (2013). Print-specific multimodal brain activation in kindergarten improves prediction of reading skills in second grade. *Neuroimage, 82*, 605-615.

Bishop, D. V., & Snowling, M. J. (2004). Developmental dyslexia and specific language impairment: Same or different? *Psychological Bulletin, 130*(6), 858.

Black, J. M., Tanaka, H., Stanley, L., Nagamine, M., Zakerani, N., Thurston, A., . . . Hoeft, F. (2012). Maternal history of reading difficulty is associated with reduced language-related gray matter in beginning readers. *Neuroimage, 59*(3), 3021-3032.

Blaiklock, K. E. (2004). The importance of letter knowledge in the relationship between phonological awareness and reading. *Journal of Research in Reading, 27*(1), 36-57.

Blau, V., Reithler, J., van Atteveldt, N., Seitz, J., Gerretsen, P., Goebel, R., & Blomert, L. (2010). Deviant processing of letters and speech sounds as proximate cause of reading failure: a functional magnetic resonance imaging study of dyslexic children. *Brain, 133*, 868-879.

Blau, V., van Atteveldt, N., Ekkebus, M., Goebel, R., & Blomert, L. (2009). Reduced neural integration of letters and speech sounds

links phonological and reading deficits in adult dyslexia. *Current Biology, 19*(6), 503-508.
Blomert, L. (2011). The neural signature of orthographic-phonological binding in successful and failing reading development. *Neuroimage, 57*(3), 695-703.
Blomert, L., & Willems, G. (2010). Is there a causal link from a phonological awareness deficit to reading failure in children at familial risk for dyslexia? *Dyslexia, 16*(4), 300-317.
Boets, B., de Beeck, H. P. O., Vandermosten, M., Scott, S. K., Gillebert, C. R., Mantini, D., . . . Ghesquière, P. (2013). Intact but less accessible phonetic representations in adults with dyslexia. *Science, 342*(6163), 1251-1254.
Bonte, M., Ley, A., Scharke, W., & Formisano, E. (2016). Developmental refinement of cortical systems for speech and voice processing. *Neuroimage, 128*, 373-384.
Bookheimer, S. Y. (2000). Methodological issues in pediatric neuroimaging. *Mental retardation and developmental disabilities research reviews, 6*(3), 161-165.
Brandeis, D., & Lehmann, D. (1986). Event-related potentials of the brain and cognitive processes: approaches and applications. *Neuropsychologia, 24*(1), 151-168.
Brem, S., Bach, S., Kucian, K., Guttorm, T. K., Martin, E., Lyytinen, H., . . . Richardson, U. (2010). Brain sensitivity to print emerges when children learn letter–speech sound correspondences. *Proceedings of the National Academy of Sciences of the United States of America, 107*(17), 7939-7944.
Brem, S., Bach, S., Kujala, J. V., Maurer, U., Lyytinen, H., Richardson, U., & Brandeis, D. (2013). An electrophysiological study of print processing in kindergarten: The contribution of the visual N1 as a predictor of reading outcome. *Developmental neuropsychology, 38*(8), 567-594.
Brem, S., Bucher, K., Halder, P., Summers, P., Dietrich, T., Martin, E., & Brandeis, D. (2006). Evidence for developmental changes in the visual word processing network beyond adolescence. *Neuroimage, 29*(3), 822-837.
Brem, S., Halder, P., Bucher, K., Summers, P., Martin, E., & Brandeis, D. (2009). Tuning of the visual word processing system: distinct developmental ERP and fMRI effects. *Human Brain Mapping, 30*(6), 1833-1844.

Brennan, C., Cao, F., Pedroarena-Leal, N., McNorgan, C., & Booth, J. R. (2013). Reading acquisition reorganizes the phonological awareness network only in alphabetic writing systems. *Human Brain Mapping, 34*(12), 3354-3368.

Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002). *Region of interest analysis using an SPM toolbox [abstract]* Presented at the 8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan.

Buchsbaum, B. R., Hickok, G., & Humphries, C. (2001). Role of left posterior superior temporal gyrus in phonological processing for speech perception and production. *Cognitive Science, 25*(5), 663-678.

Buchweitz, A. (2016). Language and reading development in the brain today: neuromarkers and the case for prediction. *Jornal de Pediatria, 92*(3), S8-S13.

Bühler, J. C., Waßmann, F., Buser, D., Zumberi, F., & Maurer, U. (2017). Neural processes associated with vocabulary and vowel-length differences in a dialect: An ERP study in pre-literate children. *Brain Topography*.

Button, K. S., Ioannidis, J. P., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S., & Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience, 14*(5), 365-376.

Calvert, G. A. (2001). Crossmodal processing in the human brain: insights from functional neuroimaging studies. *Cerebral Cortex, 11*(12), 1110-1123.

Carota, F., Kriegeskorte, N., Nili, H., & Pulvermüller, F. (2017). Representational similarity mapping of distributional semantics in left inferior frontal, middle temporal, and motor cortex. *Cerebral Cortex, 27*(1), 294-309.

Catts, H. W., Fey, M. E., Zhang, X., & Tomblin, J. B. (2001). Estimating the risk of future reading difficulties in kindergarten children: A research-based model and its clinical implementation. *Language, speech, and hearing services in schools, 32*(1), 38-50.

Clark, K. A., Helland, T., Specht, K., Narr, K. L., Manis, F. R., Toga, A. W., & Hugdahl, K. (2014). Neuroanatomical precursors of dyslexia identified from pre-reading through to age 11. *Brain, 137*(12), 3136-3141.

Cohen, L., Dehaene, S., Naccache, L., Lehéricy, S., Dehaene-Lambertz, G., Hénaff, M.-A., & Michel, F. (2000). The visual word form area. Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. *Brain, 123*(2), 291-307.

Conant, L. L., Liebenthal, E., Desai, A., & Binder, J. R. (2014). FMRI of phonemic perception and its relationship to reading development in elementary-to middle-school-age children. *Neuroimage, 89*, 192-202.

Daniel, S. S., Walsh, A. K., Goldston, D. B., Arnold, E. M., Reboussin, B. A., & Wood, F. B. (2006). Suicidality, school dropout, and reading problems among adolescents. *Journal of Learning Disabilities, 39*(6), 507-514.

Debener, S., Ullsperger, M., Siegel, M., & Engel, A. K. (2006). Single-trial EEG–fMRI reveals the dynamics of cognitive function. *Trends in cognitive sciences, 10*(12), 558-563.

Dębska, A., Łuniewska, M., Chyl, K., Banaszkiewicz, A., Żelechowska, A., Wypych, M., . . . Jednoróg, K. (2016). Neural basis of phonological awareness in beginning readers with familial risk of dyslexia—Results from shallow orthography. *Neuroimage, 132*, 406-416.

Dehaene-Lambertz, G., Dehaene, S., & Hertz-Pannier, L. (2002). Functional neuroimaging of speech perception in infants. *Science, 298*(5600), 2013-2015.

Dehaene, S. (2013). Inside the letterbox: how literacy transforms the human brain. *Cerebrum, 7*, 1-16.

Dehaene, S., & Cohen, L. (2007). Cultural recycling of cortical maps. *Neuron, 56*(2), 384-398.

Dehaene, S., Cohen, L., Sigman, M., & Vinckier, F. (2005). The neural code for written words: a proposal. *Trends in Cognitive Sciences, 9*(7), 335-341.

Dehaene, S., Pegado, F., Braga, L. W., Ventura, P., Nunes Filho, G., Jobert, A., . . . Cohen, L. (2010). How learning to read changes the cortical networks for vision and language. *Science, 330*(6009), 1359-1364.

Dilnot, J., Hamilton, L., Maughan, B., & Snowling, M. J. (2017). Child and environmental risk factors predicting readiness for learning in children at high risk of dyslexia. *Development and Psychopathology, 29*(1), 235-244.

Dirks, E., Spyer, G., van Lieshout, E. C., & de Sonneville, L. (2008). Prevalence of combined reading and arithmetic disabilities. *Journal of Learning Disabilities, 41*(5), 460-473.

Doricchi, F., Macci, E., Silvetti, M., & Macaluso, E. (2010). Neural correlates of the spatial and expectancy components of endogenous and stimulus-driven orienting of attention in the Posner task. *Cerebral Cortex, 20*(7), 1574-1585.

Duncan, C. C., Barry, R. J., Connolly, J. F., Fischer, C., Michie, P. T., Näätänen, R., . . . Van Petten, C. (2009). Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology, 120*(11), 1883-1908.

Eckert, M. (2004). Neuroanatomical markers for dyslexia: a review of dyslexia structural imaging studies. *The Neuroscientist, 10*(4), 362-371.

Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences, 113*(28), 7900-7905. doi: 10.1073/pnas.1602413113

Elben, C. E., & Lohaus, A. (2000). *Marburger Sprachverständnistest für Kinder: MSVK*. Göttingen: Hogrefe, Verlag für Psychologie.

Elbro, C., Borstrøm, I., & Petersen, D. K. (1998). Predicting dyslexia from kindergarten: The importance of distinctness of phonological representations of lexical items. *Reading Research Quarterly, 33*(1), 36-60.

Fisher, S. E., & DeFries, J. C. (2002). Developmental dyslexia: genetic dissection of a complex cognitive trait. *Nature Reviews Neuroscience, 3*(10), 767-780.

Flowers, D., Jones, K., Noble, K., VanMeter, J., Zeffiro, T., Wood, F., & Eden, G. (2004). Attention to single letters activates left extrastriate cortex. *Neuroimage, 21*(3), 829-839.

Fraga González, G., Žarić, G., Tijms, J., Bonte, M., & van der Molen, M. W. (2017). Contributions of letter-speech sound learning and visual print tuning to reading improvement: Evidence from brain potential and dyslexia training studies. *Brain Sciences, 7*(1), 10.

Freire, P., & Slover, L. (1983). The importance of the act of reading. *Journal of education, 165*(1), 5-11.

Froyen, D., Bonte, M. L., van Atteveldt, N., & Blomert, L. (2009). The long road to automation: neurocognitive development of letter–

speech sound processing. *Journal of Cognitive Neuroscience, 21*(3), 567-580.
Froyen, D., van Atteveldt, N., Bonte, M., & Blomert, L. (2008). Cross-modal enhancement of the MMN to speech-sounds indicates early and automatic integration of letters and speech-sounds. *Neuroscience letters, 430*(1), 23-28.
Froyen, D., Willems, G., & Blomert, L. (2011). Evidence for a specific cross-modal association deficit in dyslexia: an electrophysiological study of letter–speech sound processing. *Developmental science, 14*(4), 635-648.
Gabrieli, J. D., Ghosh, S. S., & Whitfield-Gabrieli, S. (2015). Prediction as a humanitarian and pragmatic contribution from human cognitive neuroscience. *Neuron, 85*(1), 11-26.
Gallagher, A., Frith, U., & Snowling, M. J. (2000). Precursors of literacy delay among children at genetic risk of dyslexia. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 41*(2), 203-213.
Galuschka, K., Ise, E., Krick, K., & Schulte-Körne, G. (2014). Effectiveness of treatment approaches for children and adolescents with reading disabilities: a meta-analysis of randomized controlled trials. *PloS one, 9*(2), e89900.
Gooch, D., Hulme, C., Nash, H. M., & Snowling, M. J. (2014). Comorbidities in preschool children at family risk of dyslexia. *Journal of Child Psychology and Psychiatry, 55*(3), 237-246.
Goswami, U. (2000). Phonological representations, reading development and dyslexia: Towards a cross-linguistic theoretical framework. *Dyslexia, 6*(2), 133-151.
Goswami, U. (2015). Sensory theories of developmental dyslexia: three challenges for research. *Nature Reviews Neuroscience, 16*(1), 43-54.
Gullick, M. M., & Booth, J. R. (2014). Individual differences in crossmodal brain activity predict arcuate fasciculus connectivity in developing readers. *Journal of Cognitive Neuroscience, 26*(7), 1331-1346.
Guttorm, T. K., Leppänen, P. H., Hämäläinen, J. A., Eklund, K. M., & Lyytinen, H. J. (2010). Newborn event-related potentials predict poorer pre-reading skills in children at risk for dyslexia. *Journal of Learning Disabilities, 43*(5), 391-401.
Guttorm, T. K., Leppänen, P. H., Poikkeus, A.-M., Eklund, K. M., Lyytinen, P., & Lyytinen, H. (2005). Brain event-related

potentials (ERPs) measured at birth predict later language development in children with and without familial risk for dyslexia. *Cortex, 41*(3), 291-303.

Habib, M. (2000). The neurological basis of developmental dyslexia. *Brain, 123*(12), 2373-2399.

Hahn, N., Foxe, J. J., & Molholm, S. (2014). Impairments of multisensory integration and cross-sensory learning as pathways to dyslexia. *Neuroscience & Biobehavioral Reviews, 47*, 384-392.

Hashimoto, R., & Sakai, K. L. (2004). Learning letters in adulthood: direct visualization of cortical plasticity for forming a new link between orthography and phonology. *Neuron, 42*(2), 311-322.

Hebb, D. O. (1949). *The organization of behavior: A neuropsychological approach*. New York: John Wiley & Sons.

Hoeft, F., McCandliss, B. D., Black, J. M., Gantman, A., Zakerani, N., Hulme, C., . . . Reiss, A. L. (2011). Neural systems predicting long-term outcome in dyslexia. *Proceedings of the National Academy of Sciences, 108*(1), 361-366.

Hoeft, F., Ueno, T., Reiss, A. L., Meyler, A., Whitfield-Gabrieli, S., Glover, G. H., . . . Jo, B. (2007). Prediction of children's reading skills using behavioral, functional, and structural neuroimaging measures. *Behavioral neuroscience, 121*(3), 602-613.

Holland, S. K., Plante, E., Byars, A. W., Strawsburg, R. H., Schmithorst, V. J., & Ball, W. S. (2001). Normal fMRI brain activation patterns in children performing a verb generation task. *Neuroimage, 14*(4), 837-843.

Holloway, I. D., van Atteveldt, N., Blomert, L., & Ansari, D. (2015). Orthographic dependency in the neural correlates of reading: evidence from audiovisual integration in english readers. *Cerebral Cortex, 25*(6), 1544-1553.

Huettel, S. A., Song, A. W., & McCarthy, G. (2009). *Functional magnetic resonance imaging* (Second Edition ed.). Sunderland, MA: Sinauer Associates, Inc

Hulme, C., Hatcher, P. J., Nation, K., Brown, A., Adams, J., & Stuart, G. (2002). Phoneme awareness is a better predictor of early reading skill than onset-rime awareness. *Journal of experimental child psychology, 82*(1), 2-28.

Huster, R. J., Debener, S., Eichele, T., & Herrmann, C. S. (2012). Methods for simultaneous EEG-fMRI: an introductory review. *Journal of Neuroscience, 32*(18), 6053-6060.

Im, K., Raschle, N. M., Smith, S. A., Grant, P. E., & Gaab, N. (2016). Atypical sulcal pattern in children with developmental dyslexia and at-risk kindergarteners. *Cerebral Cortex, 26*(3), 1138-1148.

Jacquemot, C., Pallier, C., LeBihan, D., Dehaene, S., & Dupoux, E. (2003). Phonological grammar shapes the auditory cortex: a functional magnetic resonance imaging study. *Journal of Neuroscience, 23*(29), 9541-9546.

James, K. H. (2010). Sensori-motor experience leads to changes in visual processing in the developing brain. *Developmental science, 13*(2), 279-288.

James, K. H., & Gauthier, I. (2006). Letter processing automatically recruits a sensory–motor brain network. *Neuropsychologia, 44*(14), 2937-2949.

Jobard, G., Crivello, F., & Tzourio-Mazoyer, N. (2003). Evaluation of the dual route theory of reading: a metanalysis of 35 neuroimaging studies. *Neuroimage, 20*(2), 693-712.

Jones, M. W., Kuipers, J.-R., & Thierry, G. (2016). ERPs reveal the time-course of aberrant visual-phonological binding in developmental dyslexia. *Frontiers in human neuroscience, 10*.

Karipidis, I. I., Pleisch, G., Röthlisberger, M., Hofstetter, C., Dornbierer, D., Stämpfli, P., & Brem, S. (2017). Neural initialization of audiovisual integration in prereaders at varying risk for developmental dyslexia. *Human Brain Mapping, 38*(2), 1038-1055.

Kast, M., Bezzola, L., Jäncke, L., & Meyer, M. (2011). Multi- and unisensory decoding of words and nonwords result in differential brain responses in dyslexic and nondyslexic adults. *Brain and Language, 119*(3), 136-148.

Kersey, A. J., & James, K. H. (2013). Brain activation patterns resulting from learning letter forms through active self-production and passive observation in young children. *Frontiers in psychology, 4*.

Kirby, J. R., Georgiou, G. K., Martinussen, R., & Parrila, R. (2010). Naming speed and reading: From prediction to instruction. *Reading Research Quarterly, 45*(3), 341-362.

Kraft, I., Schreiber, J., Cafiero, R., Metere, R., Schaadt, G., Brauer, J., . . . Skeide, M. A. (2016). Predicting early signs of dyslexia at a preliterate age by combining behavioral assessment with structural MRI. *Neuroimage, 143*, 378-386.

Kronschnabel, J., Brem, S., Maurer, U., & Brandeis, D. (2014). The level of audiovisual print-speech integration deficits in dyslexia. *Neuropsychologia, 62*, 245-261.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., . . . Fox, P. T. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping, 10*(3), 120-131.

Landerl, K., Ramus, F., Moll, K., Lyytinen, H., Leppänen, P. H., Lohvansuu, K., . . . Bruder, J. (2013). Predictors of developmental dyslexia in European orthographies with varying complexity. *Journal of Child Psychology and Psychiatry, 54*(6), 686-694.

Lefly, D. L., & Pennington, B. F. (2000). Reliability and validity of the adult reading history questionnaire. *Journal of Learning Disabilities, 33*(3), 286-296.

Lehmann, D., & Skrandies, W. (1980). Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalography and clinical neurophysiology, 48*(6), 609-621.

Leseman, P. P., & Jong, P. F. (1998). Home literacy: Opportunity, instruction, cooperation and social-emotional quality predicting early reading achievement. *Reading Research Quarterly, 33*(3), 294-318.

Linkersdörfer, J., Jurcoane, A., Lindberg, S., Kaiser, J., Hasselhorn, M., Fiebach, C. J., & Lonnemann, J. (2014). The association between gray matter volume and reading proficiency: a longitudinal study of beginning readers. *Journal of Cognitive Neuroscience*.

Liu, B., Wang, Z., & Jin, Z. (2009). The integration processing of the visual and auditory information in videos of real-world events: an ERP study. *Neuroscience letters, 461*(1), 7-11.

Lochy, A., Van Reybroeck, M., & Rossion, B. (2016). Left cortical specialization for visual letter strings predicts rudimentary knowledge of letter-sound association in preschoolers. *Proceedings of the National Academy of Sciences of the United States of America, 113*(30), 8544–8549.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412*(6843), 150-157.

Luck, S. J. (2005). *An introduction to the event-related potential technique.* Cambridge, MA: MIT Press.

Lyytinen, H., Erskine, J., Kujala, J., Ojanen, E., & Richardson, U. (2009). In search of a science-based application: A learning tool for reading acquisition. *Scandinavian journal of psychology, 50*(6), 668-675.

Lyytinen, H., Erskine, J., Tolvanen, A., Torppa, M., Poikkeus, A.-M., & Lyytinen, P. (2006). Trajectories of reading development: A follow-up from birth to school age of children with and without risk for dyslexia. *Merrill-Palmer Quarterly, 52*(3), 514-546.

Lyytinen, H., Ronimus, M., Alanko, A., Poikkeus, A.-M., & Taanila, M. (2007). Early identification of dyslexia and the use of computer game-based practice to support reading acquisition. *Nordic Psychology, 59*(2), 109-126.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage, 19*(3), 1233-1239.

Mandelkow, H., Halder, P., Boesiger, P., & Brandeis, D. (2006). Synchronization facilitates removal of MRI artefacts from concurrent EEG recordings and increases usable bandwidth. *Neuroimage, 32*(3), 1120-1126.

Martin, A., Kronbichler, M., & Richlan, F. (2016). Dyslexic brain activation abnormalities in deep and shallow orthographies: A meta-analysis of 28 functional neuroimaging studies. *Human Brain Mapping, 37*(7), 2676-2699.

Maurer, U., Blau, V. C., Yoncheva, Y. N., & McCandliss, B. D. (2010). Development of visual expertise for reading: rapid emergence of visual familiarity for an artificial script. *Developmental Neuropsychology, 35*(4), 404-422.

Maurer, U., Brem, S., Bucher, K., Kranz, F., Benz, R., Steinhausen, H.-C., & Brandeis, D. (2007). Impaired tuning of a fast occipito-temporal response for print in dyslexic children learning to read. *Brain, 130*(12), 3200-3210.

Maurer, U., Bucher, K., Brem, S., Benz, R., Kranz, F., Schulz, E., . . . Brandeis, D. (2009). Neurophysiology in preschool improves behavioral prediction of reading ability throughout primary school. *Biological psychiatry, 66*(4), 341-348.

Maurer, U., Bucher, K., Brem, S., & Brandeis, D. (2003). Altered responses to tone and phoneme mismatch in kindergartners at familial dyslexia risk. *Neuroreport, 14*(17), 2245-2250.

Maurer, U., Schulz, E., Brem, S., van der Mark, S., Bucher, K., Martin, E., & Brandeis, D. (2011). The development of print tuning in children with dyslexia: Evidence from longitudinal ERP data supported by fMRI. *Neuroimage, 57*(3), 714-722.

Mayer, A. (2011). *Test zur Erfassung der phonologischen Bewusstheit und der Benennungsgeschwindigkeit (TEPHOBE)*. München: Ernst Reinhardt Verlag.

Mazaika, P., Whitfield-Gabrieli, S., Reiss, A., & Glover, G. (2007). *Artifact repair for fMRI data from high motion clinical subjects.* Presented at the Organization of Human Brain Mapping International Conference, Chicago, IL.

McBride-Chang, C. (1999). The ABCs of the ABCs: The development of letter-name and letter-sound knowledge. *Merrill-Palmer Quarterly, 45*(2), 285-308.

McCandliss, B. D., Cohen, L., & Dehaene, S. (2003). The visual word form area: expertise for reading in the fusiform gyrus. *Trends in Cognitive Sciences, 7*(7), 293-299.

McNorgan, C., Awati, N., Desroches, A. S., & Booth, J. R. (2014). Multimodal Lexical Processing in Auditory Cortex Is Literacy Skill Dependent. *Cerebral Cortex, 24*(9), 2464-2475. doi: 10.1093/cercor/bht100

McNorgan, C., Randazzo-Wagner, M., & Booth, J. R. (2013). Cross-modal integration in the brain is related to phonological awareness only in typical readers, not in those with reading difficulty. *Frontiers in Human Neuroscience, 7*, 159-170.

Melby-Lervåg, M., Lyster, S.-A. H., & Hulme, C. (2012). Phonological skills and their role in learning to read: a meta-analytic review. *Psychological bulletin, 138*(2), 322-352.

Molfese, D. L. (2000). Predicting dyslexia at 8 years of age using neonatal brain responses. *Brain and Language, 72*(3), 238-245.

Moll, K., Hasko, S., Groth, K., Bartling, J., & Schulte-Körne, G. (2016). Letter-sound processing deficits in children with developmental dyslexia: an ERP study. *Clinical Neurophysiology, 127*(4), 1989-2000.

Moll, K., & Landerl, K. (2014). *Lese- und Rechtschreibtest (SLRT-II). Weiterentwicklung des Salzburger Lese- und Rechtschreibtests*

(SLRT), 2., korrigierte Auflage mit erweiterten Normen. Bern: Verlag Hans Huber.
Moll, K., Ramus, F., Bartling, J., Bruder, J., Kunze, S., Neuhoff, N., . . . Lohvansuu, K. (2014). Cognitive mechanisms underlying reading and spelling development in five European orthographies. *Learning and Instruction, 29*, 65-77.
Monzalvo, K., & Dehaene-Lambertz, G. (2013). How reading acquisition changes children's spoken language network. *Brain and Language, 127*(3), 356-365.
Mourgues, C., Tan, M., Hein, S., Ojanen, E., Reich, J., Lyytinen, H., & Grigorenko, E. L. (2016). Paired associate learning tasks and their contribution to reading skills. *Learning and Individual Differences, 46*, 54-63.
Mugnaini, D., Lassi, S., La Malfa, G., & Albertini, G. (2009). Internalizing correlates of dyslexia. *World Journal of Pediatrics, 5*(4), 255-264.
Mulert, C., Jäger, L., Schmitt, R., Bussfeld, P., Pogarell, O., Möller, H.-J., . . . Hegerl, U. (2004). Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. *Neuroimage, 22*(1), 83-94.
Myers, C. A., Vandermosten, M., Farris, E. A., Hancock, R., Gimenez, P., Black, J. M., . . . Hendren, R. L. (2014). White matter morphometric changes uniquely predict children's reading acquisition. *Psychological Science, 25*(10), 1870-1883.
Nash, H. M., Gooch, D., Hulme, C., Mahajan, Y., McArthur, G., Steinmetzger, K., & Snowling, M. J. (2017). Are the literacy difficulties that characterize developmental dyslexia associated with a failure to integrate letters and speech sounds? *Developmental science, 20*(4), 1-16.
Norton, E. S., & Wolf, M. (2012). Rapid automatized naming (RAN) and reading fluency: Implications for understanding and treatment of reading disabilities. *Annual Review of Psychology, 63*, 427-452.
Ogawa, S., Lee, T.-M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences, 87*(24), 9868-9872.

Osborne, J. W., & Overbay, A. (2004). The power of outliers (and why researchers should always check for them). *Practical assessment, research & evaluation, 9*(6), 1-12.

Ozernov-Palchik, O., & Gaab, N. (2016). Tackling the 'dyslexia paradox': reading brain and behavior for early markers of developmental dyslexia. *Wiley Interdisciplinary Reviews Cognitive Science, 7*(2), 156-176.

Ozernov-Palchik, O., Norton, E. S., Sideridis, G., Beach, S. D., Wolf, M., Gabrieli, J. D., & Gaab, N. (2016). Longitudinal stability of pre-reading skill profiles of kindergarten children: implications for early screening and theories of reading. *Developmental science*.

Paracchini, S., Scerri, T., & Monaco, A. P. (2007). The genetic lexicon of dyslexia. *Annual Review of Genomics and Human Genetics, 8*, 57-79.

Parviainen, T., Helenius, P., Poskiparta, E., Niemi, P., & Salmelin, R. (2011). Speech perception in the child brain: Cortical timing and its relevance to literacy acquisition. *Human Brain Mapping, 32*(12), 2193-2206.

Pascual-Leone, A., Freitas, C., Oberman, L., Horvath, J. C., Halko, M., Eldaief, M., . . . Rotenberg, A. (2011). Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI. [journal article]. *Brain Topography, 24*(3), 302-315.

Pascual-Marqui, R. D. (1999). Review of methods for solving the EEG inverse problem. *International journal of bioelectromagnetism, 1*(1), 75-86.

Pascual-Marqui, R. D., Michel, C. M., & Lehmann, D. (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *International Journal of Psychophysiology, 18*(1), 49-65.

Pekkola, J., Laasonen, M., Ojanen, V., Autti, T., Jaaskelainen, I. P., Kujala, T., & Sams, M. (2006). Perception of matching and conflicting audiovisual speech in dyslexic and fluent readers: An fMRI study at 3 T. *Neuroimage, 29*(3), 797-807.

Pennington, B. F., & Lefly, D. L. (2001). Early reading development in children at family risk for dyslexia. *Child Development, 72*(3), 816-833.

Pennington, B. F., Orden, G. C., Smith, S. D., Green, P. A., & Haith, M. M. (1990). Phonological processing skills and deficits in adult dyslexics. *Child Development, 61*(6), 1753-1778.

Plakas, A., van Zuijen, T., van Leeuwen, T., Thomson, J. M., & van der Leij, A. (2013). Impaired non-speech auditory processing at a pre-reading age is a risk-factor for dyslexia but not a predictor: an ERP study. *Cortex, 49*(4), 1034-1045.

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage, 10*(1), 15-35.

Poskiparta, E., Niemi, P., Lepola, J., Ahtola, A., & Laine, P. (2003). Motivational-emotional vulnerability and difficulties in learning to read and spell. *British Journal of Educational Psychology, 73*(2), 187-206.

Price, C. J., & Devlin, J. T. (2011). The Interactive Account of ventral occipitotemporal contributions to reading. *Trends in Cognitive Sciences, 15*(6), 246-253.

Pugh, K. R., Mencl, W. E., Jenner, A. R., Katz, L., Frost, S. J., Lee, J. R., . . . Shaywitz, B. A. (2001). Neurobiological studies of reading and reading disability. *Journal of Communication Disorders, 34*(6), 479-492.

Puolakanaho, A., Ahonen, T., Aro, M., Eklund, K., Leppänen, P. H., Poikkeus, A. M., . . . Lyytinen, H. (2007). Very early phonological and language skills: estimating individual risk of reading disability. *Journal of Child Psychology and Psychiatry, 48*(9), 923-931.

Raij, T., Uutela, K., & Hari, R. (2000). Audiovisual integration of letters in the human brain. *Neuron, 28*(2), 617-625.

Ramus, F. (2004). Neurobiology of dyslexia: A reinterpretation of the data. *Trends in Neurosciences, 27*(12), 720-726.

Raschle, N. M., Lee, M., Buechler, R., Christodoulou, J. A., Chang, M., Vakil, M., . . . Gaab, N. (2009). Making MR imaging child's play-pediatric neuroimaging protocol, guidelines and procedure. *Journal of Visualized Experiments*(29), e1309.

Raschle, N. M., Stering, P. L., Meissner, S. N., & Gaab, N. (2014). Altered Neuronal Response During Rapid Auditory Processing and Its Relation to Phonological Processing in Prereading Children at Familial Risk for Dyslexia. *Cerebral Cortex, 24*, 2489-2501.

Raschle, N. M., Zuk, J., & Gaab, N. (2012). Functional characteristics of developmental dyslexia in left-hemispheric posterior brain regions predate reading onset. *Proceedings of the National Academy of Sciences of the United States of America, 109*(6), 2156-2161.

Regel, S., Kotz, S. A., Henseler, I., & Friederici, A. D. (2017). Left inferior frontal gyrus mediates morphosyntax: ERP evidence from verb processing in left-hemisphere damaged patients. *Cortex, 86*, 156-171.

Richlan, F., Kronbichler, M., & Wimmer, H. (2013). Structural abnormalities in the dyslexic brain: A meta-analysis of voxel-based morphometry studies. *Human brain mapping, 34*(11), 3055-3065.

Rossion, B., Joyce, C. A., Cottrell, G. W., & Tarr, M. J. (2003). Early lateralization and orientation tuning for face, word, and object processing in the visual cortex. *Neuroimage, 20*(3), 1609-1624.

Roth, A., Roesch-Ely, D., Bender, S., Weisbrod, M., & Kaiser, S. (2007). Increased event-related potential latency and amplitude variability in schizophrenia detected through wavelet-based single trial analysis. *International Journal of Psychophysiology, 66*(3), 244-254.

Sandak, R., Mencl, W. E., Frost, S. J., & Pugh, K. R. (2004). The neurobiological basis of skilled and impaired reading: recent findings and new directions. *Scientific Studies of Reading, 8*(3), 273-292.

Saygin, Z. M., Osher, D. E., Norton, E. S., Youssoufian, D. A., Beach, S. D., Feather, J., . . . Kanwisher, N. (2016). Connectivity precedes function in the development of the visual word form area. *Nature Neuroscience, 19*(9), 1250-1255.

Scarborough, H. S. (1990). Very early language deficits in dyslexic children. *Child Development, 61*(6), 1728-1743.

Schatschneider, C., Fletcher, J. M., Francis, D. J., Carlson, C. D., & Foorman, B. R. (2004). Kindergarten prediction of reading skills: A longitudinal comparative analysis. *Journal of Educational Psychology, 96*(2), 265.

Schlaggar, B. L., & McCandliss, B. D. (2007). Development of neural systems for reading. *Annual Review of Neuroscience, 30*, 475-503.

Share, D. L. (1995). Phonological recoding and self-teaching:< i> sine qua non</i> of reading acquisition. *Cognition, 55*(2), 151-218.

Shaywitz, B. A., Skudlarski, P., Holahan, J. M., Marchione, K. E., Constable, R. T., Fulbright, R. K., . . . Shaywitz, S. E. (2007). Age-related changes in reading systems of dyslexic children. *Annals of neurology, 61*(4), 363-370.

Shaywitz, S. E., Shaywitz, B. A., Fletcher, J. M., & Escobar, M. D. (1990). Prevalence of reading disability in boys and girls: Results of the Connecticut Longitudinal Study. *JAMA, 264*(8), 998-1002.

Snowling, M. J. (1980). The development of grapheme-phoneme correspondence in normal and dyslexic readers. *Journal of experimental child psychology, 29*(2), 294-305.

Snowling, M. J. (2013). Early identification and interventions for dyslexia: a contemporary view. *Journal of Research in Special Educational Needs, 13*(1), 7-14.

Snowling, M. J., Gallagher, A., & Frith, U. (2003). Family risk of dyslexia is continuous: Individual differences in the precursors of reading skill. *Child Development, 74*(2), 358-373.

Specht, K., Hugdahl, K., Ofte, S., Nygård, M., Bjørnerud, A., Plante, E., & Helland, T. (2009). Brain activation on pre-reading tasks reveals at-risk status for dyslexia in 6-year-old children. *Scandinavian journal of psychology, 50*(1), 79-91.

Szaflarski, J. P., Holland, S. K., Schmithorst, V. J., & Byars, A. W. (2006). fMRI study of language lateralization in children and adults. *Human brain mapping, 27*(3), 202-212.

Terry, N. P., Connor, C. M., Thomas-Tate, S., & Love, M. (2010). Examining relationships among dialect variation, literacy skills, and school context in first grade. *Journal of Speech, Language, and Hearing Research, 53*(1), 126-145.

Thesen, T., McDonald, C. R., Carlson, C., Doyle, W., Cash, S., Sherfey, J., . . . Devinsky, O. (2012). Sequential then interactive processing of letters and words in the left fusiform gyrus. *Nature communications, 3*, 1-8.

Tilanus, E. A., Segers, E., & Verhoeven, L. (2013). Diagnostic profiles of children with developmental dyslexia in a transparent orthography. *Research in developmental disabilities, 34*(11), 4194-4202.

Torppa, M., Poikkeus, A.-M., Laakso, M.-L., Tolvanen, A., Leskinen, E., Leppanen, P. H., . . . Lyytinen, H. (2007). Modeling the early paths of phonological awareness and factors supporting its development in children with and without familial risk of dyslexia. *Scientific Studies of Reading, 11*(2), 73-103.

Tyler, L. K., Marslen-Wilson, W. D., Randall, B., Wright, P., Devereux, B. J., Zhuang, J., . . . Stamatakis, E. A. (2011). Left inferior frontal cortex and syntax: function, structure and behaviour in patients with left hemisphere damage. *Brain, 134*(2), 415-431.

van Atteveldt, N., & Ansari, D. (2014). How symbols transform brain function: A review in memory of Leo Blomert. *Trends in Neuroscience and Education, 3*(2), 44-49.

van Atteveldt, N., Formisano, E., Goebel, R., & Blomert, L. (2004). Integration of letters and speech sounds in the human brain. *Neuron, 43*(2), 271-282.

van Bergen, E., de Jong, P. F., Maassen, B., & van der Leij, A. (2014). The effect of parents' literacy skills and children's preliteracy skills on the risk of dyslexia. *Journal of Abnormal Child Psychology, 42*(7), 1187-1200.

van Herten, M., Pasman, J., van Leeuwen, T. H., Been, P. H., van der Leij, A., Zwarts, F., & Maassen, B. (2008). Differences in AERP responses and atypical hemispheric specialization in 17-month-old children at risk of dyslexia. *Brain Research, 1201*, 100-105.

van Zuijen, T. L., Plakas, A., Maassen, B. A., Been, P., Maurits, N. M., Krikhaar, E., . . . van der Leij, A. (2012). Temporal auditory processing at 17 months of age is associated with preliterate language comprehension and later word reading fluency: an ERP study. *Neuroscience Letters, 528*(1), 31-35.

Vandermosten, M., Boets, B., Poelmans, H., Sunaert, S., Wouters, J., & Ghesquière, P. (2012). A tractography study in dyslexia: neuroanatomic correlates of orthographic, phonological and speech processing. *Brain, 135*(3), 935-948.

Vandermosten, M., Hoeft, F., & Norton, E. S. (2016). Integrating MRI brain imaging studies of pre-reading children with current theories of developmental dyslexia: a review and quantitative meta-analysis. *Current Opinion in Behavioral Sciences, 10*, 155-161.

Vinckier, F., Dehaene, S., Jobert, A., Dubus, J. P., Sigman, M., & Cohen, L. (2007). Hierarchical coding of letter strings in the ventral stream: dissecting the inner organization of the visual word-form system. *Neuron, 55*(1), 143-156.

Waberski, T. D., Kreitschmann-Andermahr, I., Kawohl, W., Darvas, F., Ryang, Y., Rodewald, M., . . . Buchner, H. (2001). Spatio-temporal source imaging reveals subcomponents of the human auditory mismatch negativity in the cingulum and right inferior temporal gyrus. *Neuroscience letters, 308*(2), 107-110.

Wagner, R. K., & Torgesen, J. K. (1987). The nature of phonological processing and its causal role in the acquisition of reading skills. *Psychological bulletin, 101*(2), 192-212.

Wagner, R. K., Torgesen, J. K., & Rashotte, C. A. (1994). Development of reading-related phonological processing abilities: New evidence of bidirectional causality from a latent variable longitudinal study. *Developmental Psychology, 30*(1), 73.

Wechsler, D. (2011). *Wechsler Intelligence Scale for Children (WISC-IV)* (Fourth Edition ed.). Frankfurt am Main: Pearson Assessment & Information GmbH.

West, M., & Chew, H. E. (2014). *Reading in the mobile era: A study of mobile reading in developing countries*. 7, place de Fontenoy, 75352 Paris 07 SP, France: United Nations Educational, Scientific and Cultural Organization.

Whelan, R., & Garavan, H. (2014). When optimism hurts: inflated predictions in psychiatric neuroimaging. *Biological Psychiatry, 75*(9), 746-748.

Widmann, A., Schröger, E., Tervaniemi, M., Pakarinen, S., & Kujala, T. (2012). Mapping symbols to sounds: electrophysiological correlates of the impaired reading process in dyslexia. *Frontiers in psychology, 3*, 1-12.

Wild, N., & Fleck, C. (2013). Neunormierung des Mottier-Tests für 5- bis 17-jährige Kinder mit Deutsch als Erst-oder als Zweitsprache. *Praxis Sprache, 3*, 152-158.

Wilke, M., & Holland, S. K. (2003). Variability of gray and white matter during normal development: a voxel-based MRI analysis. *Neuroreport, 14*(15), 1887-1890.

Wilke, M., Holland, S. K., Altaye, M., & Gaser, C. (2008). Template-O-Matic: a toolbox for creating customized pediatric templates. *Neuroimage, 41*(3), 903-913.

Willems, G., Jansma, B., Blomert, L., & Vaessen, A. (2016). Cognitive and familial risk evidence converged: A data-driven identification of distinct and homogeneous subtypes within the heterogeneous sample of reading disabled children. *Research in Developmental Disabilities, 53*, 213-231.

Wimmer, H. (2006). Don't neglect reading fluency! *Developmental science, 9*(5), 447-448.

Xia, Z., Hancock, R., & Hoeft, F. (2017). Neurobiological bases of reading disorder Part I: Etiological investigations. *Language and Linguistics Compass, 11*(4), 1-18.

Yoncheva, Y. N., Blau, V. C., Maurer, U., & McCandliss, B. D. (2010). Attentional focus during learning impacts N170 ERP responses to an artificial script. *Developmental Neuropsychology, 35*(4), 423-445.

Yoncheva, Y. N., Wise, J., & McCandliss, B. (2015). Hemispheric specialization for visual words is shaped by attention to sublexical units during initial learning. *Brain and Language, 145–146*, 23-33.

Žarić, G., González, G. F., Tijms, J., van der Molen, M. W., Blomert, L., & Bonte, M. (2014). Reduced neural integration of letters and speech sounds in dyslexic children scales with individual differences in reading fluency. *PLoS ONE, 9*(10), e110337.

Žarić, G., González, G. F., Tijms, J., van der Molen, M. W., Blomert, L., & Bonte, M. (2015). Crossmodal deficit in dyslexic children: practice affects the neural timing of letter-speech sound integration. *Frontiers in Human Neuroscience, 9*, 1-14.

Zhao, L., Chen, C., Shao, L., Wang, Y., Xiao, X., Chen, C., . . . Xue, G. (2016). Orthographic and phonological representations in the fusiform cortex. *Cerebral Cortex*.

Ziegler, J. C., Bertrand, D., Tóth, D., Csépe, V., Reis, A., Faísca, L., . . . Blomert, L. (2010). Orthographic depth and its impact on universal predictors of reading a cross-language investigation. *Psychological Science, 21*(4), 551-559.

Ziegler, J. C., & Goswami, U. (2005). Reading acquisition, developmental dyslexia, and skilled reading across languages: a psycholinguistic grain size theory. *Psychological bulletin, 131*(1), 3-29.

Curriculum Vitae

	PERSONAL INFORMATION
Name	Iliana Irini Karipidis
Date of birth	March 8, 1988
Nationalities	Swiss and Greek
	EDUCATION
Since 08/2013	**Doctorate at the Department of Psychology**, *University of Zurich* **Neuroscience Center Zurich (ZNZ) doctoral program**, *University of Zurich and ETH Zurich*
06-09/2013	**Qualified User Training**, *Magnetic Resonance Imaging Centre of the University Hospital of Psychiatry Zurich*
09/2010-01/2013	**Master of Science in Psychology**: Cognitive Psychology and cognitive neuroscience, *University of Zurich*
06-09/2011	**Internship**, *Department of Neurology – Clinical Neuropsychology, Charité Universitätsmedizin Berlin*, Germany
10/2006-06/2010	**Bachelor of Science in Psychology**, *University of Zurich*
10/2005-07/2006	**Undergraduate studies in Psychology**, *Panteion University of social and political sciences*, Athens, Greece
	EMPLOYMENT HISTORY
Since 06/2013	**PhD Candidate Position**, *Department of Child and Adolescent Psychiatry and Psychotherapy, University Hospital of Psychiatry Zurich*, Prof. Silvia Brem

03-06/2013	**Exhibition Supervisor**, *Life Science Communication AG*, Zurich
03-06/2013	**Sales and Marketing Assistant**, *YouRehab*, Zurich
10/2011-01/2013	**Research Assistant**, *Cognitive Psychology Unit*, *University of Zurich*, Prof. Klaus Oberauer
07/2008-03/2012	**Office Administrator**, *Swiss Association for Energy Economics*, Zurich
12/2007-03/2012	**Research and Teaching Assistant**, *Centre for Energy Policy and Economics*, *ETH Zurich*, Prof. Massimo Filippini

PRIZES, AWARDS, FELLOWSHIPS

06/2016 & 06/2015	ZNZ Student Travel Grant for the 21st & 22nd Annual Meeting of the Organization for Human Brain Mapping
08/2015	Best Poster Award at the 11th Zurich Center for Integrative Human Physiology Symposium
06-09/2011	Erasmus Program Scholarship

PUBLICATIONS IN PEER-REVIEWED SCIENTIFIC JOURNALS

Karipidis, I. I., Pleisch, G., Röthlisberger, M., Dornbierer, D., Hofstetter, C., Stämpfli, P., Brem, S. (2017). Neural initialization of audiovisual integration in prereaders at varying risk for developmental dyslexia. Human Brain Mapping, 38(2), 1038-1055.

Brem, S., Hunkeler, E., Mächler, M., Kronschnabel, J., *Karipidis, I. I.*, Pleisch, G., Brandeis, D. (2017). Increasing visual expertise to a novel script modulated the visual N1 ERP in healthy adults. International Journal of Behavioral Development, accepted.

Strombach, T., Weber, B., Hangebrauk, Z., Kenning, P., *Karipidis, I. I.*, Tobler, P. N., Kalenscher, T. (2015). Social discounting involves modulation of neural value signals by temporoparietal junction. Proceedings of the National Academy of Sciences, 112(5), 1619-1624.

UNPUBLISHED WORK

Karipidis, I.I., Pleisch, G., Brandeis, D., Roth, A., Röthlisberger, M., Schneebeli, M., Walitza, S., Brem, S. (2017). Simulating reading acquisition: a multimodal neuroimaging approach to predict reading fluency. Prepared for submission.

Pleisch, G., *Karipidis, I. I.*, Brauchli, C., Röthlisberger, M., Hofstetter, C., Stämpfli, P., Brem, S. (2017). Neural specialization to characters in the prereading brain. Under revision.

Soutschek, A., Burke, C. J., Beharelle, A. R., Schreiber, R., Weber, S. C., *Karipidis, I. I.*, ten Velden, J., Weber, B., Haker, H., Kalenscher, T., Tobler, P. N. (2017). Dopaminergic reward system underpins gender differences in social preferences. Under revision.

PEER-REVIEWED CONFERENCE PROCEEDINGS

Karipidis, I. I., Pleisch, G., Röthlisberger, M., Hofstetter, C., Dornbierer, D., Stämpfli, P., Brem, S.: Neural initialization of audiovisual integration in prereaders at varying risk for developmental dyslexia. Poster presentation at the 3rd Burghölzli Psychiatry Meeting, Zurich 10/2016.

Karipidis, I. I., Pleisch, G., Röthlisberger, M., Stämpfli, P., Hofstetter, C., Brem, S.: Development of speech and letter processing in children at risk for developmental dyslexia. Poster presentation at the 22nd Annual Meeting of the Organisation for Human Brain Mapping, Geneva 06/2016.

Röthlisberger, M., *Karipidis, I. I.*, Pleisch, G., Dellwo, V., Richardson, U., Brem, S.: Swiss GraphoGame: Concept and design presentation of a computerised reading intervention for children with hight risk for poor reading outcomes. Paper at the 16th Annual Conference of the International Speech Communication Association, Dresden 09/2015.

Karipidis, I. I., Pleisch, G., Röthlisberger, M., Stämpfli, P., Walitza, S., Brandeis, D., Brem, S.: Initial grapheme-phoneme integration in prereading children with a familial risk for developmental dyslexia. Poster presentation at the 11th ZIHP Symposium, Zurich 08/2015.

Karipidis, I. I., Pleisch, G., Röthlisberger, M., Stämpfli, P., Hofstetter, C., Brem, S.: Grapheme-phoneme integration in the temporal cortex of the prereading brain. Poster presentation at the 21st Annual Meeting of the Organisation for Human Brain Mapping, Honolulu 06/2015.

Karipidis, I. I., Pleisch, G., Röthlisberger, M., Stämpfli, P., Walitza, S., Brandeis, D., Brem, S.: Initial grapheme-phoneme integration in prereading children with a familial risk for developmental dyslexia. Poster presentation at the XXXIV. DGKJP-Kongress, Munich 03/2015.

Karipidis, I. I., Pleisch, G., Röthlisberger, M., Brauchli, C., Bauer, A., Dornbierer, D., Schneebeli, M., Stämpfli, P., Brem, S.: Audiovisual integration in the prereading brain. Poster presentation at the 1st Burghölzli Psychiatry Meeting, Zurich 10/2014.

Karipidis, I. I., Strombach, T., Kalenscher, T., Tobler, P. N.: The neural basis of social discouting in comparison with temporal discounting. Poster presentation at the 1st Zurich Computational Psychiatry Meeting, Zurich 05/2014.

ORAL CONTRIBUTIONS TO CONFERENCES

5th International Congress of Educational Sciences and Development, Santander 05/2017: Simulation of letter acquisition initializes neural specialization in prereaders at risk for dyslexia.

XXXV. DGKJP-Kongress, Ulm 03/2017: A neuroimaging approach to identify prereaders struggling to learn grapheme-phoneme correspondences.